SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medical Oncology

Gestational Trophoblastic Tumours: Experience of the Oncology Department of the Moulay Ismail Military Hospital in Meknes (10 Cases)

M. Toreis[1*], A. Z. Bazine[1], Y. Touimri[1], M. Fetohi[1]

[1]Docteur Mehdi Toreis, Department of Medical Oncology, Military Hospital of Meknes- Morocco

DOI: https://doi.org/10.36347/sasjm.2024.v10i10.047 | **Received:** 07.09.2024 | **Accepted:** 16.10.2024 | **Published:** 21.10.2024

***Corresponding author:** M. Toreis
Docteur Mehdi Toreis, Department of Medical Oncology, Military Hospital of Meknes- Morocco

Abstract **Original Research Article**

Gestational trophoblastic tumors (GTTs) are the malignant forms of gestational trophoblastic diseases. They always follow a pregnancy, most often molar. The diagnosis of GTT is based on an abnormal course of HCG (chorionic gonadotropin hormone) and/or signs of ultrasound invasion and/or histological confirmation. We report a retrospective series of 10 cases of GTT collected at the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes over an 8-year period from January 2012 to January 2020. The analysis of our series led to the conclusion that: The average age of onsetis 42 years. 90% of our patients were pauciparic. The causal pregnancy was in 90% of the cases a molar pregnancy. The extension assessment was mainly based on the TAP CT identifying the lung as the main metastatic site in 40% of cases. 5 patients (50% of cases) underwent hysterectomy with post operative chemotherapy. 60% of our patients were classified as low risk according to the FIGO score and received methotrexate mono-chemotherapy. 4 patients were classified as high-risk and were treated with poly chemotherapy, the main protocol of which was EMA-CO. All our patients benefited from clinical and biological monitoring, before each chemotherapy session; then weekly and monthly after negativation, up to 12 months in case of good prognosis GTT, and up to 18 months in case of bad prognosis GTT. One case of MTX relapse (the case of IPTT) was reported and for which a 2nd line CMT with a favourable evolution was indicated. This study allowed us to analyze the cure rate, which was 100% for patients who were treated and had completed their monitoring.

Keywords: Gestational trophoblastic tumor - Invasive Mole - Choriocarcinoma - Implant Site Tumor - FIGO Score - Treatment.

I. INTRODUCTION

Gestational trophoblastic tumours (GTT) are the malignant forms of gestational trophoblastic disease.

They encompass a spectrum of lesions with a wide range of biological behaviour and a risk of metastasis; ranging from benign lesions (hydatidiform mole with its 2 variants: complete and partial) to malignant lesions which constitute gestational trophoblastic tumours including:

- Invasive moles (IM)
- Choriocarcinoma (CC)
- Trophoblastic tumours of the implantation site (TTSI)
- Epithelioid trophoblastic tumours (ETT)

GTT always occurs in the aftermath of a pregnancy, whether a molar pregnancy, spontaneous miscarriage or childbirth.

The diagnosis is made when serum levels of total choriogonadotropin (ßhCG) fail to normalise or rise again after evacuation of a hydatidiform mole, or when there is unexplained persistent metrorrhagia after a spontaneous abortion or voluntary termination of pregnancy (IVG).

GTT is a rare condition, with an incidence of 1 in 1000 live births in Europe and 1 in 1500 in the USA [1].

In Morocco, they account for 15% of GBMs, with an incidence of 1/170 deliveries. The average age of onset is 32 years. The causal pregnancy was a molar pregnancy in 65% of cases.

GTTs have a high metastatic potential and are fatal if left untreated, so chemotherapy and/or surgery are sometimes required.

These tumours are highly chemo-sensitive, requiring multidisciplinary management, and in order to give patients the best possible chance of cure, an initial assessment and the establishment of prognostic scores are used to specify the therapeutic indications.

We report a retrospective series of 10 cases of GTT collected in the oncology department of the Moulay Ismail Military Hospital in Meknes over an 8-year period from 01 January 2012 to 01 January 2020.

The objectives of our study are:

- To present the literature on the diagnosis, treatment and prognosis of this condition.
- Report the results of our study in terms of epidemiological, clinical, therapeutic and prognostic data.
- Draw up an analysis of the results obtained in our study.
- Compare our results with the literature.

II. MATERIALS AND METHODS

1. Type of study

This is a retrospective study spread over a period of 8 years, from January 2012 to January 2020, and covering 10 cases of gestational trophoblastic tumours treated and monitored in the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes.

2. Inclusion Criteria

All patients aged ≥18 years who were diagnosed with GTT after follow-up of hydatidiform mole, as well as those whose diagnosis was based on anatomopathological examination of an aspiration or curettage product and/or on anatomopathological examination of surgical parts of total hysterectomy for haemostatic purposes, or referred from other hospital structures for specialised management of GTT within the Medical Oncology Department of the Moulay Ismail Military Hospital were included in our study.

The diagnostic criteria used to make the diagnosis of GTT are those proposed in 2000 by the FIGO Oncology Committee.

3. Data Collection

Patients were recruited from the hospitalization register in the Medical Oncology Department archive. File data were collected and recorded on a pre-established data processing form (appendix), then entered into a computer database.

4. Items analysed

Our study consisted of an analysis:

a. Epidemiological profile: patient age, origin, marital status.
b. Gynaecological and obstetrical profile: gestational age, parity, history of abortion, contraception.
c. Diagnostic criteria used:
   i. Clinical and biological according to FIGO criteria.
   ii. Ultrasound
   iii. Anatomopathology
d. Classification and Prognostic Score.
e. Therapeutic protocol: type of surgery and indication, chemotherapy and protocol, specifying the number of courses.
f. The means and pace of surveillance.
g. Prognosis and fertility post-GTT.

5. Statistical analysis

The data collected were entered and recorded in Excel 2007 and analysed using SPSS statistical software.

III. RESULTS

1. EPIDEMIOLOGICAL DATA

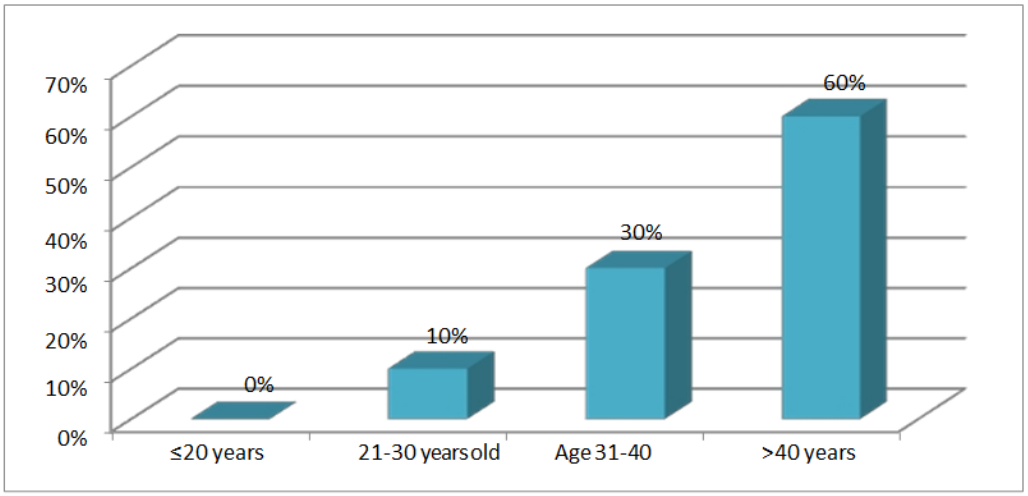
Between January 2012 and January 2020, we admitted 10 cases of GTT to the medical oncology department of the Moulay Ismail Military Hospital in Meknes.

2. Maternal age

Women aged over 40 were the most affected, with a frequency of 60% (Table 1, Graph 1). The average age was 42, with extremes of 24 and 53.

Table 1: Distribution of patients according to age

MATERNAL AGE	NUMBER OF CASES	FREQUENCY
≤ 20	0	0%
21-30	1	10%
31-40	3	30%
> 40	6	60%
Total	10	100%



Graph 1: Distribution of patients according to age

a. Paternal age

This parameter was not mentioned in any of the files.

b. Geographical origin

6 patients were from urban areas, and 4 patients were from rural areas, giving approximate frequencies for geographical origin (Graph 2).

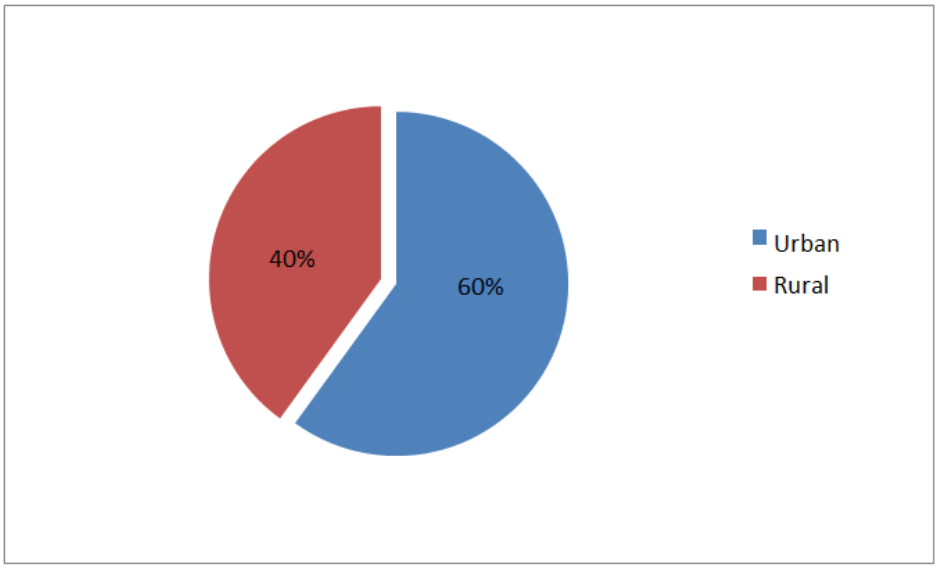


Figure 2: Breakdown of patients by origin

c. Marital status

All our patients were married when they were admitted to the department.

d. Socio-economic level

The majority of our patients were of low socio-economic status, with a frequency of 80%.

e. Blood grouping

This parameter was not mentioned in our patients' files.

3. ANTECEDENTS

One patient had a history of hydatidiform mole which had been aspirated 3 years before the onset of TTG. The rest of the patients had no particular history.

4. GYNECO-OBSTETRICAL PROFILE

a. Menarche:

Menarche was mentioned in only 3 patients, with 2 patients aged 12 and one patient aged 13.

b. Gestité

There is a peak in the frequency of paucigests (2-4), who account for 50% of cases, while multigestates and large multigestates account for frequencies of 40% and 10% respectively (Graph 3\ Table 2).

Table 2: Distribution of patients according to gestational age

GESTITE	WORKFORCE	FREQUENCY
1	0	0%
2-4	5	50%
5-6	4	40%
≥7	1	10%
TOTAL	10	100%

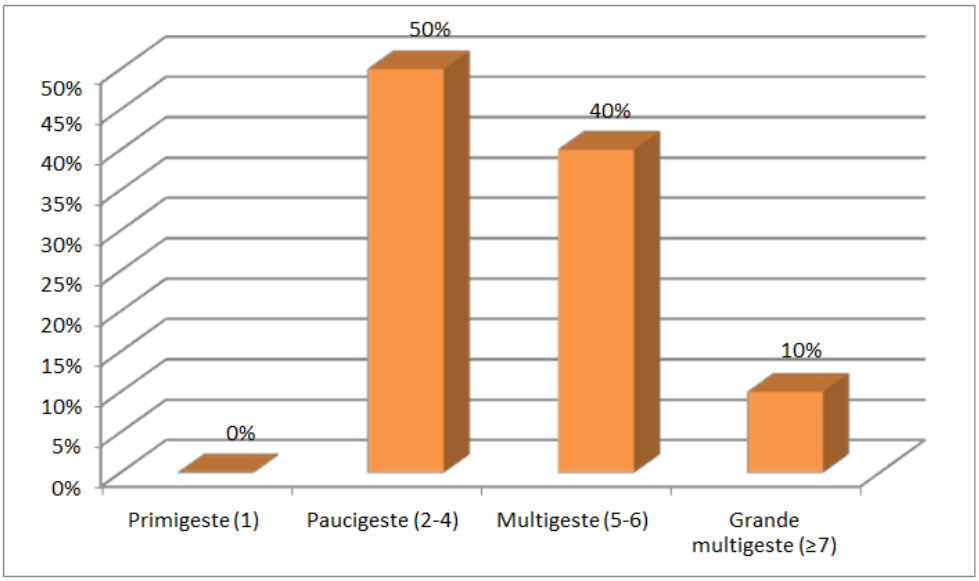


Figure 3: Distribution of patients according to gestational age

c. Parity

There was a peak in the frequency of pauciparous pregnancies, which accounted for the majority of cases, with a rate of 90%, while only one patient was multiparous, representing 10% of cases (Table 4).

However, none of the patients in our series was nulliparous or primiparous.

Table 3: Distribution of patients according to parity

PARITY	WORKFORCE	FREQUENCY
1	0	0%
2-4	9	90%
5-6	1	10%
≥7	0	0%
TOTAL	10	100%

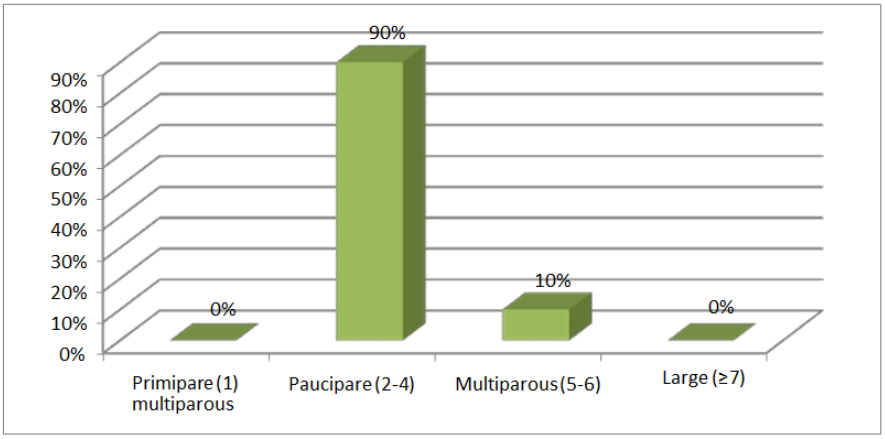


Figure 4: Distribution of patients according to parity

d. Causal pregnancy

During the study period, 10 cases of TTG were recorded, with:

i. 7 patients following complete mole, i.e. 70% of cases.
ii. 2 patients following partial mole, i.e. 20% of cases.
iii. 1 patient following an abortion, i.e. 10% of cases.

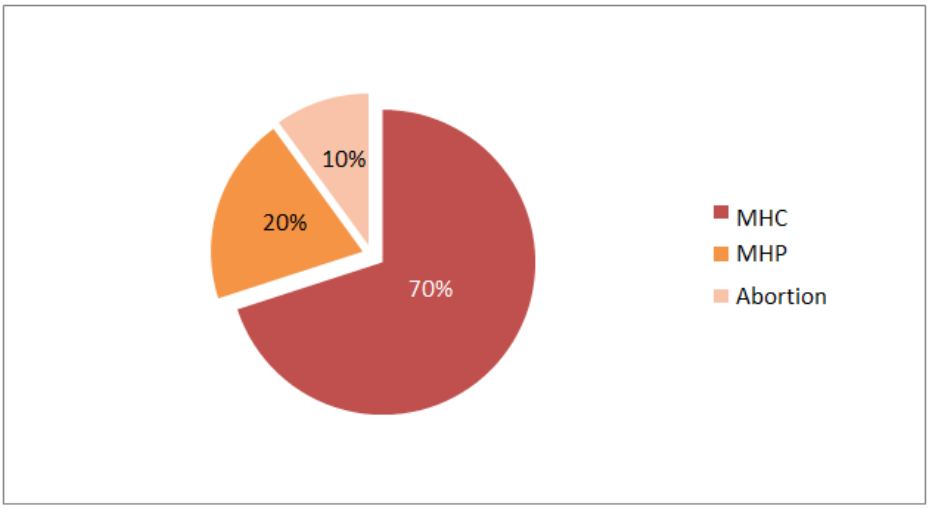


Figure 5: Distribution of patients according to causal pregnancy

e. Concept of contraception

Only 3 patients were on oral contraception before the onset of TTG, i.e. 30% of cases. The majority wanted to become pregnant (7 patients), i.e. 70% of cases.

5. POSITIVE DIAGNOSIS

a. The clinic

Breakthrough bleeding was the main revealing symptom, occurring in 7 patients, i.e. 70% of the cases.

b. Biology

5 patients, i.e. 50% of cases, were diagnosed with TTG following mole according to FIGO 2000 criteria, on the basis of the existence of an increase (variation of less than 10%) in β hCG values on at least 3 successive determinations over a period of 2 weeks (D1, D7, D14).

c. Anatomopathology

There were 5 cases of GTT initially diagnosed on anatomopathological evidence from a haemostasis hysterectomy specimen;

Objectivising in this way:

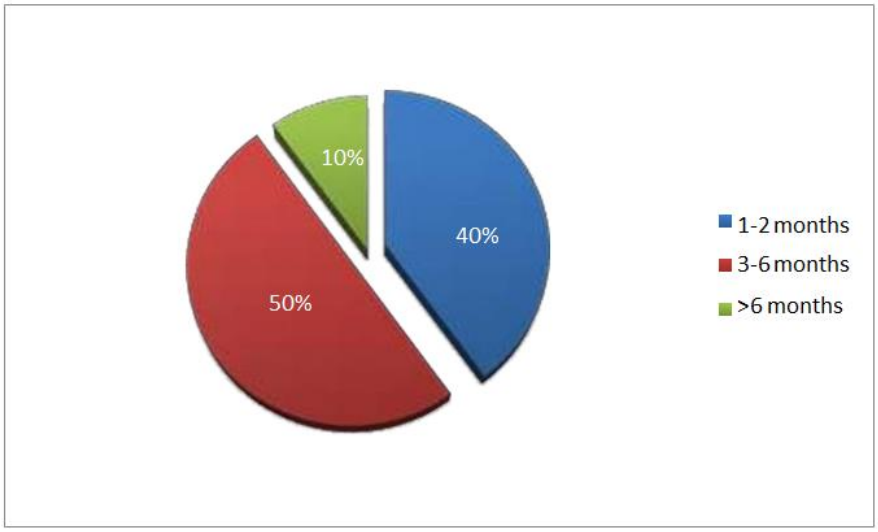
- 3 cases of invasive mole.
- 1 case of choriocarcinoma.
- 1 case of IPTT: initially diagnosed on the basis of abnormal kinetics of β hCG levels after evacuation of a molar pregnancy; however, the patient had worsened her clinical symptoms, with heavy metrorrhagia, and was referred to the department gynaecology-obstetrics department, where she underwent a haemostasis hysterectomy, the anatomopathological report of which was in favour of IPT.

d. Radiology

All patients had undergone pelvic Doppler ultrasound, which showed an enlarged uterus with a heterogeneous intramyometrial image vascularised by Doppler and no luteal cysts.

e. Delay between causal pregnancy and onset of GTT

The time to onset of GTT was between 3 and 6 months after the causal pregnancy for 5 patients, i.e. 50% of cases, between 1 and 2 months for 4 patients, i.e. 40% of cases, and after 6 months of the causal pregnancy for 1 patient, i.e. 10% of cases (Figure 6).



Graph 6: Percentage of cases according to time to onset of GTT by in relation to the causal pregnancy

f. Diagnostic criteria used

In our centre, the positive diagnosis is based on the FIGO criteria. This means that the diagnosis was based on the disturbed evolution of β hCG after complete evacuation of the uterus in 50% of patients, on histological examination in 50% of patients with 30% invasive mole, 10% choriocarcinoma and 10% IPTT (Table 4).

Table 4: Distribution of patients according to diagnostic criteria

FIGO CRITERION	WORKFORCE	FREQUENCY
BIOLOGY: CINETICS BHCG	5	50%
HISTOLOGY: INVASIVE MOLE	3	30%
HISTOLOGY: CHORIOCARCINOMA	1	10%
HISTOLOGY: TSIP	1	10%
TOTAL	10	100%

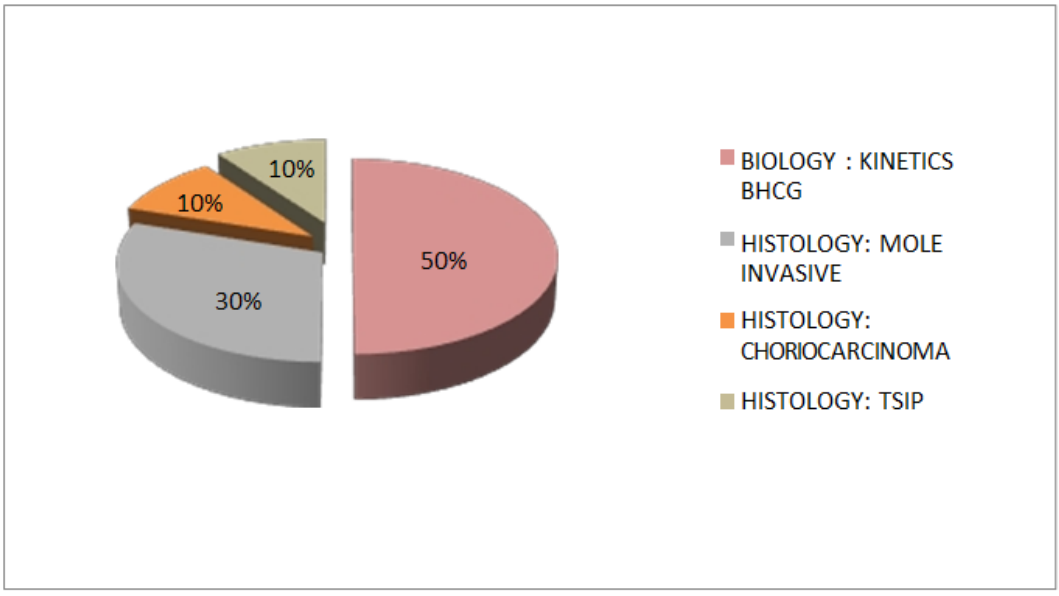


Figure 7: Distribution of patients according to diagnostic criteria

6. ASSESSMENT OF EXTENSION

All our patients underwent systematic pelvic ultrasound + Doppler, lung X-ray, abdomino-pelvic and thoracic CT scans as part of the extension work-up.

Cerebral CT was requested in 4 patients, i.e. 40% of cases, while pelvic MRI was requested in 2 patients whose CT showed invasion of the parameters by the uterine tumour.

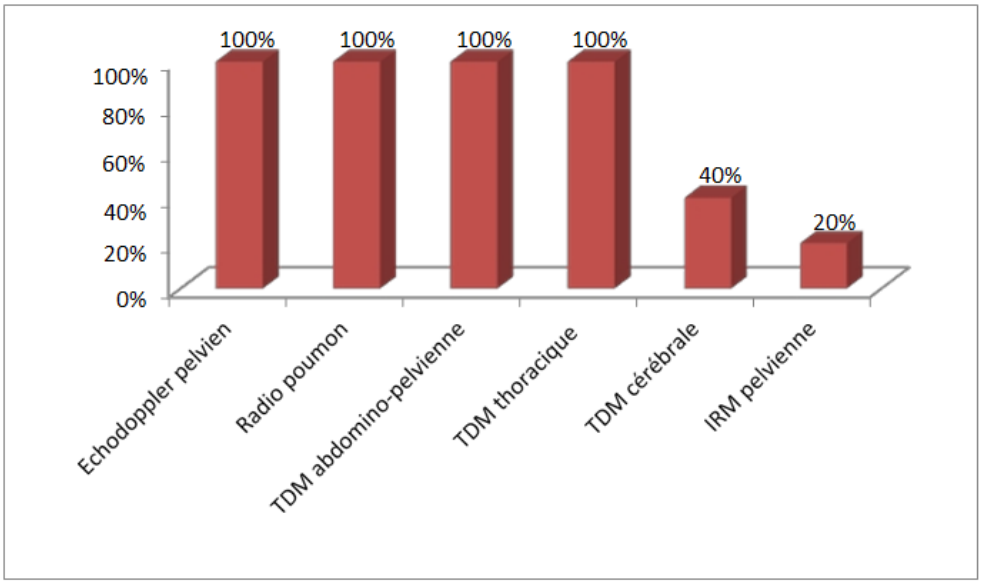


Figure 8: Distribution of patients according to extension work-up

7. METASTATIC PROFILE

In our series, 4 patients had metastases, i.e. 40% of cases, with the lung being the main metastatic site, accounting for 40% of cases. One patient presented a hepatic metastasis. No brain or vaginal metastases were found (Table 5).

Table 5: Distribution of patients according to metastatic site

METASTATIC SITE	WORKFORCE	FREQUENCY
LIP	4	40%
LIVER	1	10%
BRAIN	0	0%
VAGIN	0	0%
TOTAL	4	40%

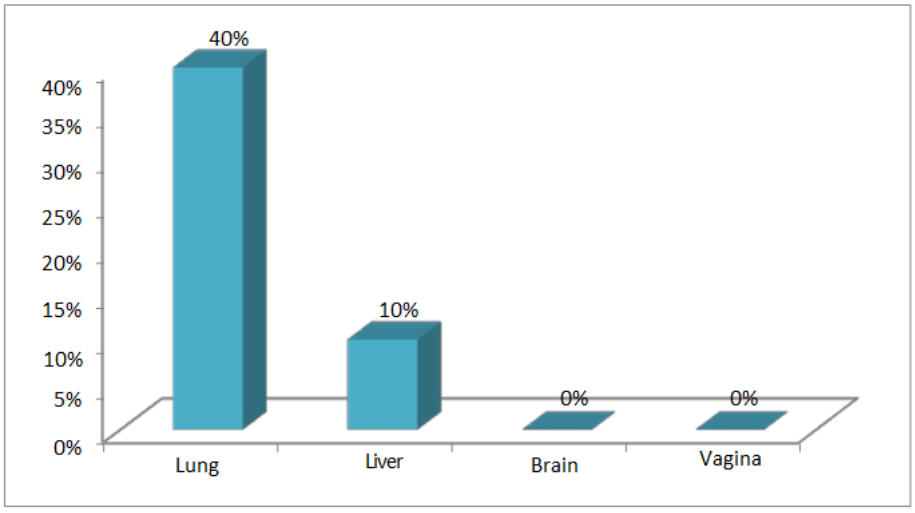


Figure 9: Distribution of patients according to metastatic site

8. PROGNOSIS SCORE

In our centre, prognostic classification is based on the FIGO 2000 prognostic score. Our scores varied between 3 and 10, the majority of our patients were low risk (score ≤6) i.e. 60% and 4 patients were scored as high risk (score ≥7) i.e. 40%.

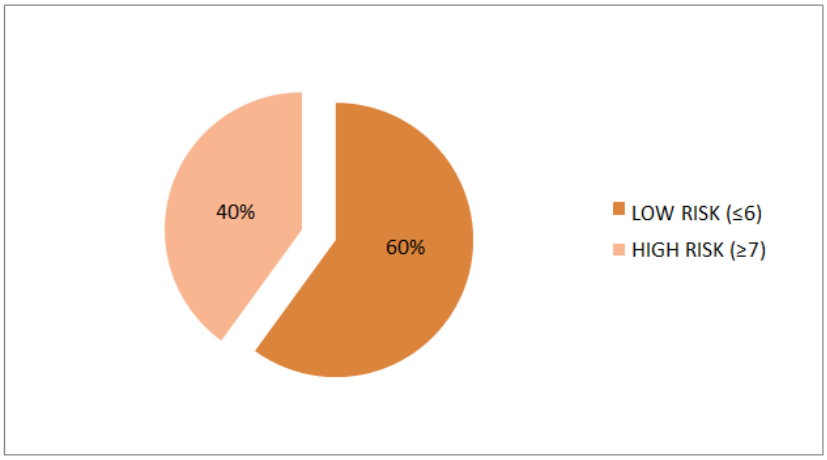


Figure 10: Distribution of patients according to FIGO 2000 prognosis score

9. THERAPEUTIC MANAGEMENT

The treatment of patients depended on their FIGO 2000 prognostic scores, and they all systematically benefited from a pre-therapeutic work-up, after a complete clinical examination, consisting of:

- Blood count (CBC)
- Complete blood ionogram
- Liver transaminases (ASAT-ALAT)
- Renal function (blood urea, creatinemia)
- Haemostasis test consisting of a PT and TCK.
- Examination required to prescribe contraception.

This assessment was also carried out before each course of chemotherapy.

a. Terms and conditions:

a. Chemotherapy (CMT):

All our patients had received chemotherapy adapted to their prognostic scores.

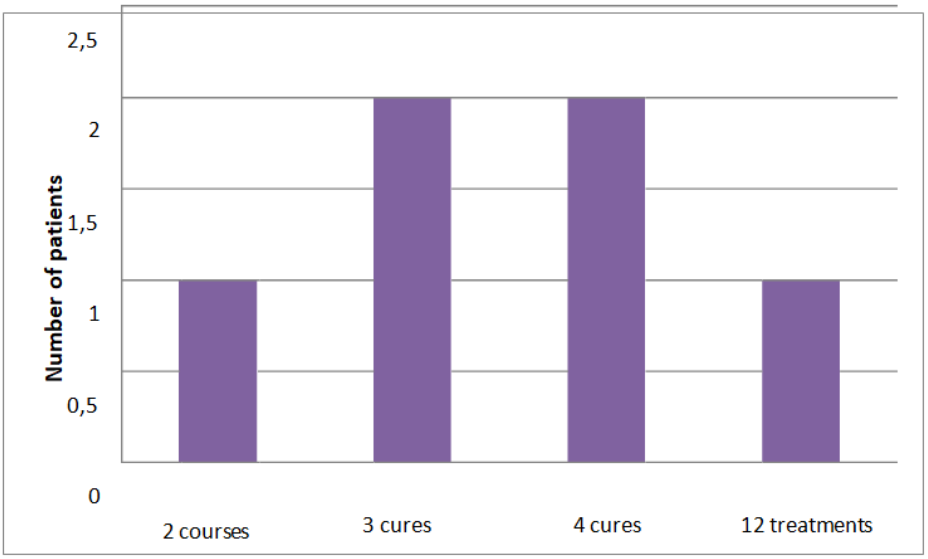
❖ For patients scored as low risk (score ≤6):

- 3 patients benefited from a protocol based on monochemotherapy carried out in our department: methotrexate (1mg/kg IM on days 1, 3, 5 and 7) alternating with folic acid (failing this, folinic acid) at a dose of 0.1mg/kg/d on days 2, 4, 6 and 8. Every 14 days until β hCG levels are negative, followed by consolidation with two courses of the same treatment regimen.
- 3 patients received CMT based on weekly IM methotrexate 40mg/m²/week until β hCG negativation, followed by 2 additional courses.

The average number of treatments received was 4.7, with a minimum of 2 and a maximum of 12 (Graph 11).

In the case of placental insertion site tumour (PIST): After hysterectomy, the patient had received 12 courses of weekly MTX-based monoCMT.

The graph below shows the distribution of our patients according to the number of treatments received; consolidation treatments are not illustrated.



Graph 11: Distribution of patients who received MTX according to the number of courses

❖ For patients scored at high risk (score ≥7):
- All patients (4 cases) received the same protocol based on multidrug therapy: EMA-CO

- D1+D2: (EMA)
- Actinomycin D 0.5 mg IV D1, D2
- Etoposide 100 mg/m² IV D1, D2
- Methotrexate 100 mg/m² IV then 200 mg/m² over 12 hrs,
- Folinic acid 15 mg IM x 2/d 12 hours after the end of MTX; 4 IVL injections 12 hours apart.

- D8: (CO)
- Vincristine 1mg/m² IV.
- Cyclophosphamide 600 mg/m² IV.

⇨ Weekly until normalisation of β hCG then consolidation: 2 courses

The average number of treatments received was 4.5, with a minimum of 4 and a maximum of 6 (Graph 12).

The graph below shows the distribution of patients who received polyCMT according to the number of courses, consolidation courses are not illustrated.

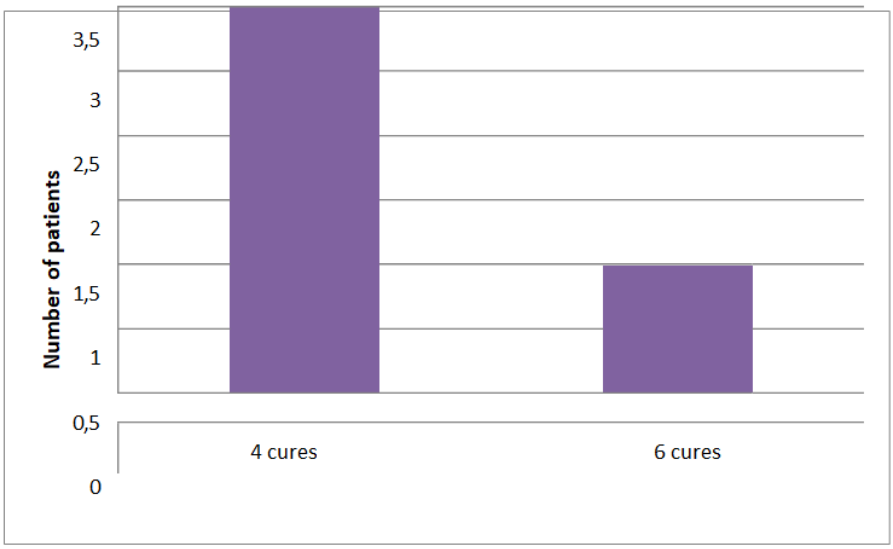


Figure 12: Distribution of patients having received polyCMT according to the number of courses of treatment

- 2nd line chemotherapy

In the case of IPT: she showed a re-ascension of β hCG levels during monitoring, after having received 12 courses of MTX, and for whom a 2nd line CMT Type EMA-CO was indicated.

- Toxicity and side effects

2 patients had experienced side-effects on administration of chemotherapy (i.e. 20% of cases) and were treated with EMA-CO: nausea/vomiting and mucositis treated symptomatically with complete recovery, and haematotoxicity, i.e. febrile neutropenia in both patients (postponement of the treatment for one week with follow-up CBC and temperature monitoring).

b. Surgery:

Hysterectomy for haemostatic purposes was performed in 5 patients.

- In the case of placental insertion site tumour: Initially, the patient was diagnosed with TTG on the basis of the disturbed kinetic evolution of β hCG levels, but the patient had worsened her metrorrhagia from which she was transferred to the gynaecology-obstetrics emergency department, where she underwent a haemostasis hysterectomy, the anatomopathological study of which confirmed the diagnosis of IPTT.

c. Embolisation

None of the patients in our series underwent embolisation.

d. Radiotherapy

None of the patients in our series underwent radiotherapy.

b. Response to treatment

All the patients have been regularly monitored in our training centre, have been declared cured and have so far shown no abnormalities.

No patients were lost to follow-up and no deaths were reported.

In the case of the placental insertion site tumour: She achieved negative β hCG levels after receiving 3 courses of EMA-CO type PolyCMT, followed by 2 consolidation courses. Progress was favourable.

10. SURVEILLANCE

For the 10 patients treated in our department, monitoring was based on:

✓ The clinic: A thorough history and clinical examination are carried out systematically at each consultation, including an abdominal, pleuropulmonary and gynaecological examination (speculum + TV).

✓ Biology: Monitoring is based on repeated determinations of serum β-hCG, at the same laboratory, at the following intervals:

- Once a week during chemotherapy and for the following 8 weeks.
- Every 15 days for the next 8 weeks.
- Then every month for up to 12 months in the case of GTT classified as low risk (good prognosis), and for up to 18 months in the case of GTT classified as high risk (poor prognosis).
- For the majority of our patients, this rhythm was respected. We also monitor during treatment by:
- CBC to detect neutropenia and thrombocytopenia.
- Liver work-up to check for hepatotoxicity.

✓ Radiology:

- An imaging study covering all the pathological sites in the initial work-up is carried out three months after the hCG levels have returned to normal.
- A pelvic and endovaginal ultrasound scan after hCG negativation and three, six and 12 months later.
- Investigations based on the warning signs.
- This assessment may reveal the persistence of residual masses. These masses may regress spontaneously and should not be surgically treated, as hCG negativity is a sign of healing.

11. POST TTG FERTILITY

Pregnancy is not authorised in our training programme until one year after the end of biological monitoring. All our patients are systematically put on contraception, except those who have had a hysterectomy.

Only 1 patient became pregnant 2 years after the end of surveillance, and her pregnancy and delivery proceeded normally without maternal or foetal complications.

IV. DISCUSSION

1. EPIDEMIOLOGY AND RISK FACTORS

a. Epidemiology

In the literature, the data found is much more relevant to MTGs in general than to TTGs.

The frequency of MTGs is extremely variable because the definition of populations at risk is particularly heterogeneous [2].

Depending on the study, the frequency is given in terms of the number of deliveries, pregnancies, live births or even abortions.

According to the literature, the incidence of GTT is highest in South-East Asia (China and Indonesia) at 1:240 deliveries [3], while it is estimated to be moderate in South America (Mexico and Brazil) at 1:500 to 1,000 deliveries, and minimal in the United States [189] and Europe at 1:2,500 deliveries [2].

In Africa, the incidence also varies significantly between countries; at the University Hospital in Tunis, the incidence was recently estimated at 1/918 deliveries [4], and 1/660 deliveries in Senegal [5].

The incidence of malignant transformation to TTG is estimated at between 10 and 20% in China [6] and 20% in the USA [18], and in France the incidence is estimated at 16% of complete moles and 0.5% of partial moles [19].

The risk of developing choriocarcinoma appears to increase considerably in Asian and Indian-American populations [7, 8].

In our series, the majority of GTTs were noted following mole.

Complete, i.e. a frequency of 70%, while 20% of cases after partial mole, and 10% of cases after abortion.

In the literature, the incidence of choriocarcinoma varies widely from country to country, with a high incidence in Asia (1/1400 [9]), the USA (1/40,000 [10]) and France (1/40,000 [11]).

The frequency of invasive mole in different countries is only assessed in a recent study in 2016 in the Slovak Republic, which corresponds to 1/101569 deliveries [12].

The incidence of each histological entity (invasive mole, choriocarcinoma) cannot be determined in our department because the diagnostic criteria are based essentially on biological disturbances, whereas anatomopathological studies were not carried out in all our patients.

IPTT is a rare entity, with 100 cases reported in the literature; in our series we noted only one case.

b. Risk factors

The risk factors identified for GTT are maternal age under 20 or over 40. A previous molar pregnancy

represents a 1% risk of recurrence, and 25% if there is more than one previous molar pregnancy [13].

MH increases the risk of choriocarcinoma, with a relative risk of 2500 after MH compared with a normal pregnancy. There are 10 to 20% of GTTs after evacuation of a HCM, compared with only 0.5% after a PHM [14]. After a molar pregnancy, the average time to onset of GTT is six months. The patient's blood group may also be a risk factor [15].

b.1 Maternal age

In our series, the incidence of GTT is highest in the 40+ age group (60% of cases), which corresponds to the age of perimenopause and menopause.

An epidemiological update [16] based on an analysis of 18 international studies identifies advanced maternal age as a major risk factor for GTT. The relative risk increases by a factor of 7.8 after the age of 40. This may be explained by genetic factors, in particular oocyte ageing, carotene and vitamin A deficiency, which favour fertilisation anomalies, and by a reduced maternal immunological response [16].

This is in perfect agreement with our study, in which 60% of patients were aged over 50 40 years old.

The relative risk of choriocarcinoma is multiplied by 1.4 in women over the age of 25 rises to 10.8 over the age of 39 [16]. According to two Senegalese and Tunisian studies, the risk of choriocarcinoma is increased after the age of 35 and 40 respectively [5, 4].

b.2 Paternal age:

This factor could not be determined in our study. In the literature, t h e inclusion of paternal age as a risk factor remains controversial.

While in most studies paternal age does not appear to have an influence, Parazzini *et al*., found a high incidence in men aged over 45 [17].

b.3 Socio-economic level and geographical origin

A low socio-economic level associated with malnutrition, essentially vitamin A and B9 deficiencies, has been suspected. However, it is obviously difficult to determine the respective impact of each of these factors [2].

In our series, the majority of our patients were of low socio-economic status and from an urban environment.

b.4 Blood type

The patient's blood group is also thought to be an important factor, with a higher risk for group A or AB patients than for group B or O patients [20-22], but no pathophysiological mechanism has been put forward to explain this observation.

Blood grouping was not mentioned in any of our patients, so a comparison with other studies cannot be made.

According to Mohammad Jafari R *et al*., [22], there is a significant relationship between blood groups (O+ and A+) and the occurrence of gestational trophoblastic tumours, particularly invasive mole and choriocarcinoma. Couples in which the woman is group A and the partner is also group A or O have a higher risk compared with other possible combinations (relative risk= 1.1-2.8) [15, 22].

b.5 Gynaecological and obstetrical history

✓ Gestité-Parité

An increase in the risk of GTT with parity is almost always reported.

Andria Altieri *et al*., [15] reported a significant increase in the risk of choriocarcinoma with parity and estimated that the risk was multiplied by 5.2 after the fourth parity.

The same notion was reported in a study in Senegal [5], where large multiparous women were three times more likely to develop choriocarcinoma than those with a parity of 4 or less.

However, more recent studies, in particular that carried out by Tchégnikin M in 2011, have concluded that the pregnancy/parity profile of patients with the disease has changed of TTG, since it found younger nulliparous patients followed by pauciparous patients. In our series, 50% of cases were paucigravida, and 40% of cases were multigravida.

The distribution according to parity shows a predominance among the poor, with a frequency of 90% of the population studied, which is in line with recent data in the literature.

✓ Pregnancy history outside the causal pregnancy

A history of abortion triples the risk of hydatidiform mole, but this factor remains debated [23]. However, there does appear to be a genetic predisposition since recurrences are not always consecutive and do not always occur with the same partner.

It is now generally accepted that the existence of a previous mole multiplies the risk of recurrence of mole by 10%, and that two previous moles increase the risk by 15 to 28% [2].

However, the influence of this history of pregnancy on malignant transformation has not yet been studied.

In our study, 1 case had a history of hydatidiform mole outside the causal pregnancy, representing 10% of our patients.

None of our patients had a history of abortion outside the causal pregnancy.

✓ Causal pregnancy

In the literature, 50% of GTTs occur following a molar pregnancy, 25% after abortion and 25% after a pregnancy carried to term [19, 24, 25]. More specifically, invasive mole complicates 10 to 20% of hydatidiform moles and 0.5% of partial moles [19, 26]. Conversion to choriocarcinoma occurs less frequently: 2-3% from complete mole and <0.5% from partial mole [27].

In parallel with the literature, the results of our study show that more than half of our patients presented with GTT following complete mole, i.e. a frequency of 70% of cases, compared with 20% following partial mole and 10% following abortion (Table 6).

Table 6: Causal pregnancy of TTG in the literature

Region	History of mole (complete or partial)	Previous abortion	Previous childbirth	Unknown causal pregnancy
France [19]	79%	11%	8.5%	0.5%
Norway [45]	75%	14%	11%	-
CHU Rabat [48]	75%	9.5%	11.5%	3.2%
Our series	90%	10%	-	-

✓ Contraception:

Oral contraception does not appear to play a role in the incidence of choriocarcinoma, but an American study concluded that the risk of this tumour increased from 2.2 to 6.4 in patients who had already taken contraception compared with those who had never taken it [15].

Stone and Kardana found a higher relative risk (RR) for the development of GTT in users of oestrogenic oral contraception [28].

A relationship between the duration of use of oral contraception and the occurrence of GTT was discussed by Palmer JR, Rosenberg L, in a study published in 1999, which showed that the longer the duration of use of oral contraception before conception, the higher the risk of occurrence of GTT [29].

In our study, only 3 patients were on oestroprogestogenic oral contraception, i.e. 30%. The duration of use was not specified.

2. ANATOMOPATHOLOGY

2.1 Invasive mole

Also known as infiltrative hydatidiform mole, chorioadenoma destruens, malignant hydatidiform mole and mola destruens.

a. Macroscopy

Infiltrative mole is a haemorrhagic mass embedded in the uterine wall [30], which may rupture the uterus, spread to the parametrium and invade the peritoneum. Distant metastases are rare, mainly in the lung, vagina, vulva and brain [31].

b. Microscopy

The tumour mass contains molar vesicles infiltrating the myometrium (image 3). Trophoblastic proliferation of the vesicles is the norm. Some vesicles may penetrate the uterine venous plexus [32].

Pathological confirmation of invasive mole can only be made on the hysterectomy specimen, or on metastasis [2].

Invasive mole must be distinguished from complete mole, placenta accreta and percreta, exuberant placental site and its variants (placental site nodule or plaque), implantation site tumour and choriocarcinoma [32].

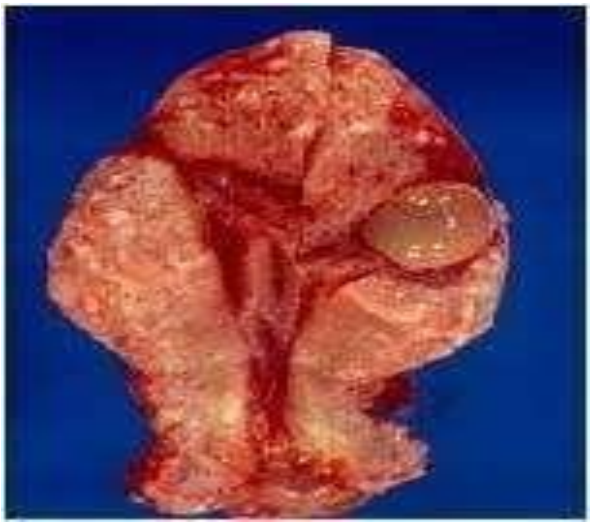


Image 1: Macroscopic appearance - presence within the myometrium of molar villi

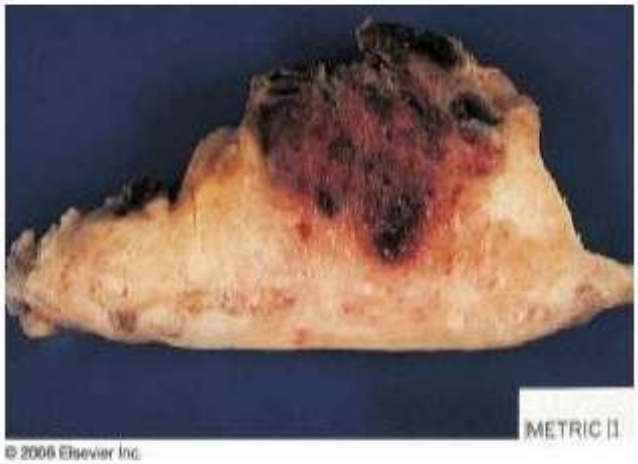


Image 2: Macroscopic appearance of the IM (one of IM haemorrhagic mass infiltrating half the thickness of the myometrial wall)

In fact, the presence of villi within the myometrium in the lumen of the vessels makes it possible to rule out complete hydatidiform mole [2].

Placenta accreta or percreta and the exuberant placental site are characterised by the presence of normal or involuted villi within the myometrium [33]. Placental implant site tumour and choriocarcinoma have neither villi nor molar vesicles [32].

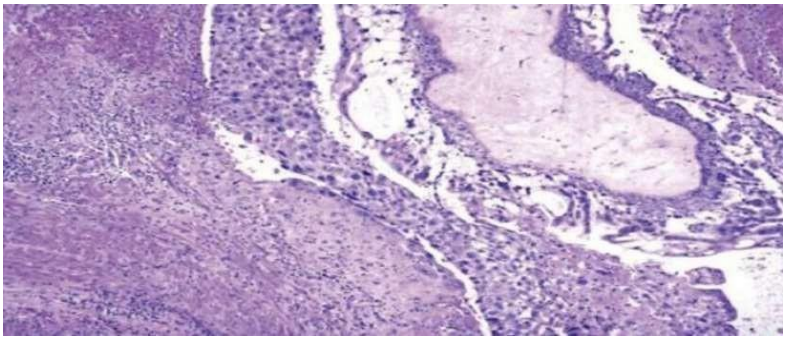


Image 3: Direct invasion of the myometrium by molar tissue including hydropic villi covered with hyperplastic trophoblast [13]

2.2 Gestational choriocarcinoma

a. Macroscopy

Gestational choriocarcinoma is represented by nodular lesions which are usually well circumscribed [34], intracavitary and/or intramural, extremely haemorrhagic and often necrotic. Its size varies from a few millimetres to more than 10cm, and it can completely fill the uterine cavity [32].

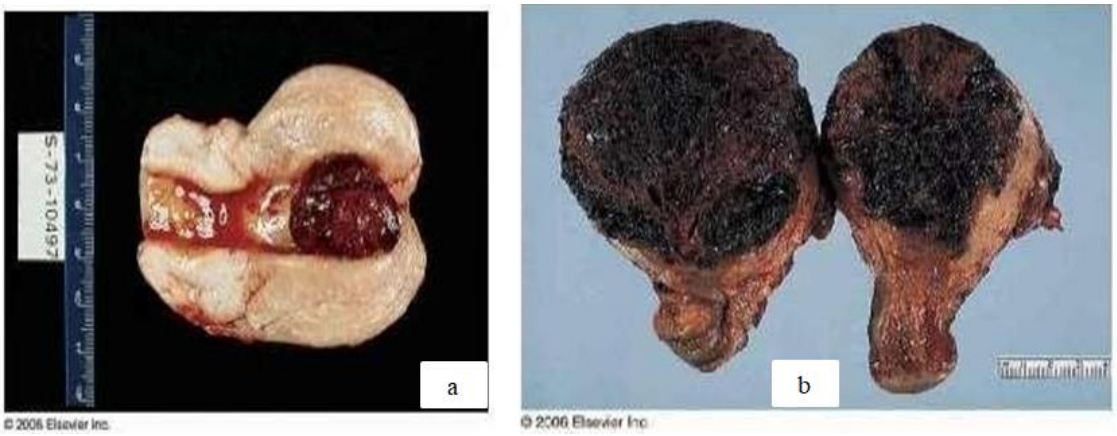


Image 4: Macroscopic appearance of an early (a) and advanced (b) stage uterine choriocarcinoma with the typical highly haemorrhagic appearance [33]

b. Microscopy (image 5)

This tumour proliferation is described as biphasic, including mononucleated cells identified as intermediate trophoblasts and multinucleated cells of the syncytiotrophoblast type in variable proportion. These different elements retain their own morphological and immunohistochemical characteristics, but with more or less marked nuclear atypia. These elements border blood lakes and destroy vascular walls, which explains the haemorrhagic and necrotic changes essentially central [34].

It is generally accepted that there should be no identifiable residual placental villi at diagnosis except in choriocarcinomas arising in a mature placenta [35-37].

Mitotic activity and proliferation index are high but do not appear to be prognostic factors [34].

Choriocarcinoma poses the problem of differential diagnosis, especially with persistent retention after molar aspiration, placental implantation site tumour, as well as epithelioid trophoblastic tumour and undifferentiated carcinoma, for which immunohistochemical study enables the tumour to be typed using appropriate antibodies. Non-gestational choriocarcinoma at the level of a metastasis also presents a differential diagnosis to choriocarcinoma. Its gestational origin will be supported by the anamnesis and possibly by evidence of the paternal genome in the tumour cells.

Syncitiotrophoblastic elements infiltrate the myometrium, colonise the vessels and migrate to distant sites. Metastatic sites are, in descending order, the lung (80%), vagina (30%), pelvis (20%), brain (20%) and liver (10%); other sites (gastrointestinal, renal, mediastinal and splenic) are exceptional [32].

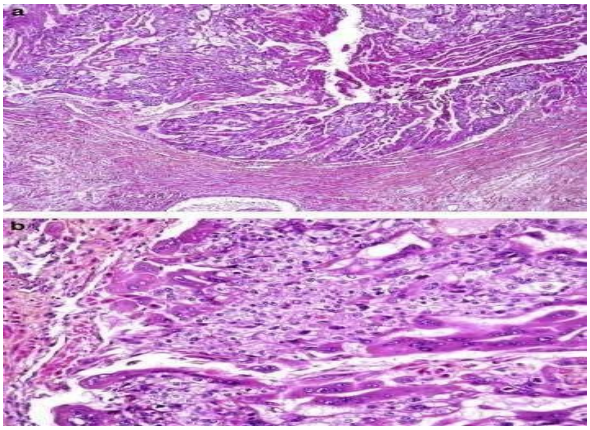


Image 5: Microscopic appearance of choriocarcinoma: biphasic proliferation without placental villi infiltrating the myometrium (a: HES × 20), composed of mononuclear cells surrounded by syncytiotrophoblastic cells (b: HES × 200) [38]

2.3 Placental implant site tumour

a. Macroscopy

It may present as an endocavitary polyp or a large nodular intramyometrial tumour, sometimes poorly limited [39, 40] and may infiltrate the entire uterine wall with extension to the broad ligament or adnexa. It appears yellowish-white with small foci of mainly necrotic or, more rarely, haemorrhagic changes [41].

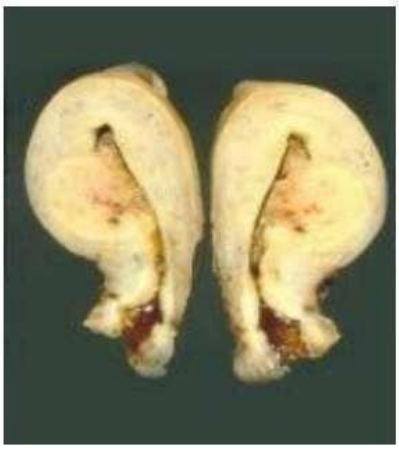


Image 6: Total hysterectomy specimen. Voluminous growing tumour intramural and intracavitary, yellowish in colour and relatively well-limited

b. Microscopy

They are characterised by the presence of an extracellular eosinophilic fibrinoid substance and by very specific vascular invasion similar to that seen in normal implantation [42] and little vascular invasion [41].

The cells are grouped in nests or trabeculae which infiltrate the myometrium at the periphery, dissociating the muscle fibres. They have the morpho-functional characteristics of the intermediate trophoblasts at the implantation site, but do not share their immunohistochemical characteristics. The cytoplasm is abundant, slightly eosinophilic, with polyhedral, rounded or occasionally fusiform outlines. They are usually mononucleated with polymorphic nuclei punctuated by a prominent nucleolus, but there may be a few multi-nucleated cells. Mitoses are few, less than 5/10 x 400 fields. Some lesions appear histologically more aggressive, with marked cytonuclear atypia and mitotic activity, and are accompanied by necrosis. Mitotic activity greater than 5/10 fields x 400 has been associated with a higher risk of recurrence [42]. For other authors, high mitotic activity or extensive necrosis do not seem to be associated with a worse prognosis [43].

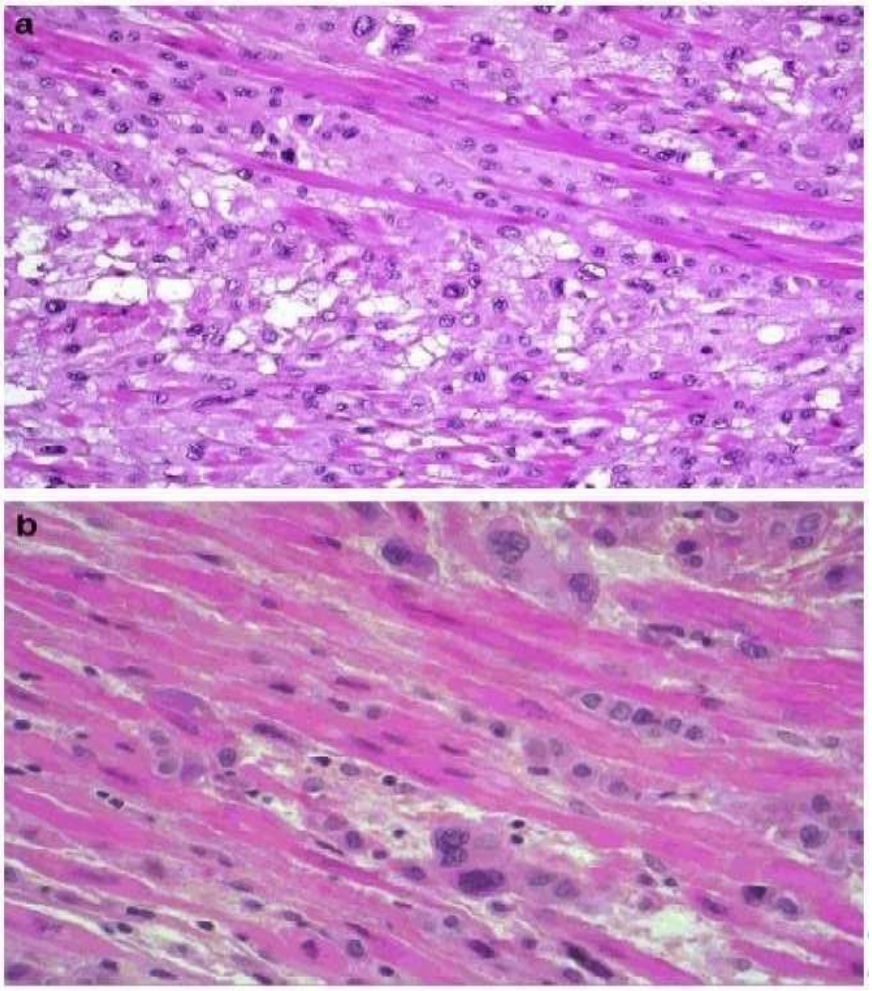


Image 7: Trophoblastic lesions of the implantation site; Trophoblastic tumour of the implantation site (a: HES × 200) composed of polygonal cells with eosinophilic or clarified cytoplasm with a central and atypical nucleus, which infiltrate the myometrium in clusters, dissociating the smooth muscle bundles without generating a stroma-desmoplastic reaction. Exaggerated reaction of the implantation site (b: HES × 400) with atypical intermediate trophoblastic cells infiltrating the myometrium individually without cluster formation [38]

The coexistence of the mixed component associating IPTT and choriocarcinoma or TTE, as well as the association of choriocarcinoma and TTE have been reported in the literature.

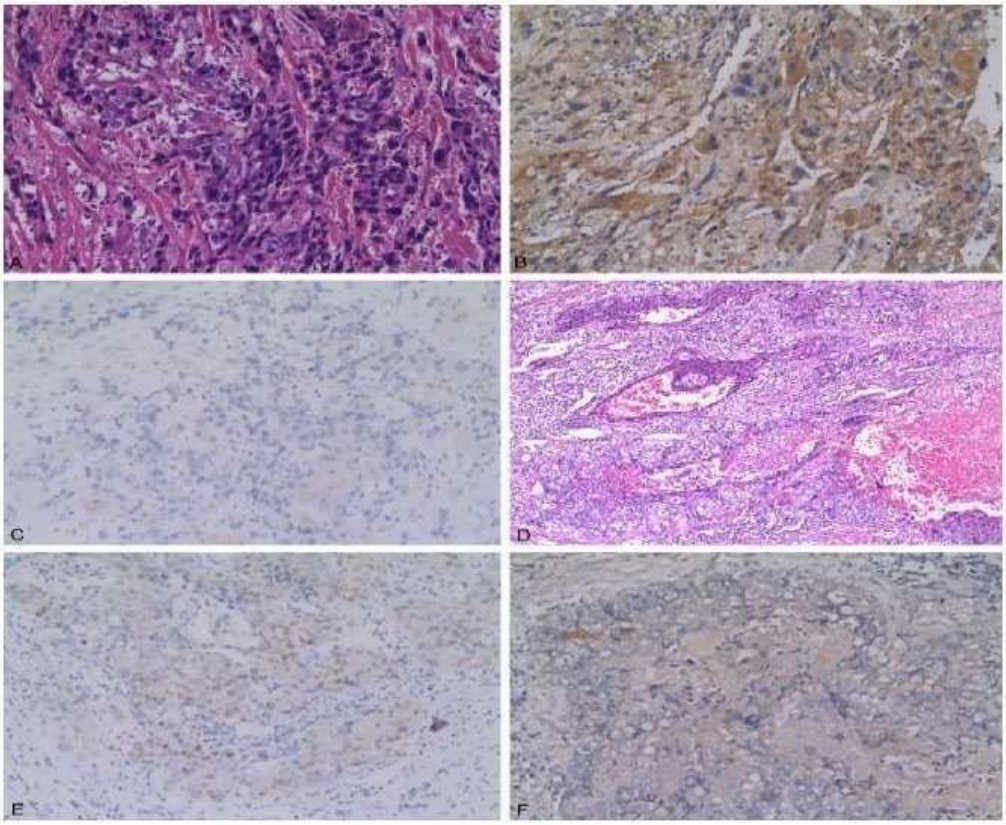


Image 8: Coexistence of TTSIP and TTE; A: The tumour is composed of bands and cords of monomorphic intermediate trophoblastic cells with abundant eosinophilic cytoplasm. They are polygonal and polymorphous. They invaded the myometrium in the cords of cells, dissecting and separating the smooth muscle bundles. B: Immunohistochemistry showed diffuse positive staining for HPL. C: negative for p63. D: Focal nodular lesion consisting of relatively uniform epithelioid cells arranged in nests. These tumour cells have a regular outline, clear cytoplasm and relatively uniform round nuclei with fine chromatin. Multi-nucleated cells were occasionally found. Dense eosinophilic hyaline material and necrotic debris in the periphery or centre of neoplastic cells in nests; E: Immunohistochemistry showed moderate staining for P63. F: MEL-CAM and focal HPL, positive or negative

2.4 Epithelioid trophoblastic tumour

a. Macroscopy

It is a nodular lesion, sometimes up to 5 cm in size, which appears prolapsed in the uterine cavity. It is located in the uterine fundus, the lower segment of the uterus or the endocervix. On section, it is heterogeneous, solid or cystic. The solid areas appear yellow or brown, with areas of necrosis and haemorrhage.

Image 9: Macroscopic appearance of the epithelioid tumour located in the segment inferior uterus, extending towards the endocervix and invading the entire uterine wall [44]

b. Microscopy

It is generally well circumscribed but may have an infiltrative tendency in the periphery [13]. The cellular patches are organised in trabeculae or clusters with contours cut out in a characteristic "geography map" fashion within a hyaline, fibrinonecrotic and eosinophilic matrix [44] which may suggest keratin. These florid tumour clusters are organised around vessels that are

occasionally modified by fibrinoid deposits but are not invaded. The tumour elements are monomorphic and mononucleated, with eosinophilic or clarified cytoplasm because they are glycogen-rich. The cell outlines are very clear. The nuclei remain small and rounded. Chromatin is dispersed and rarely contains prominent nucleoli.

Morphologically, these cells resemble chorionic-type intermediate trophoblasts with free membranes and nodules of the placental site. Mitotic activity is highly variable, averaging two mitoses per field at x 400 magnification and Ki 67 marks 5 to 25% of cells [44].

Morphologically and immunohistologically typical aspects of choriocarcinoma have been associated with MHC [44]. The epithelioid component could be responsible for chemoresistance when choriocarcinoma is diagnosed, hence the need to characterise this lesion.

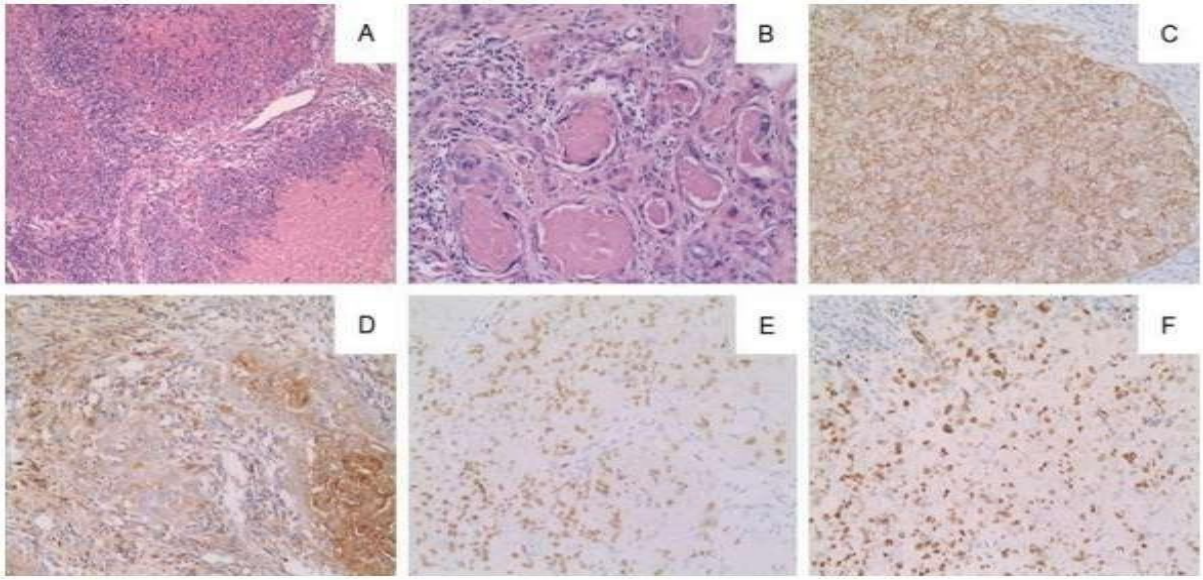


Image 10: Epithelioid trophoblastic tumour (ETT); (A) Tumour displays mononucleated trophoblastic intermediate cells, a geographical distribution of necrosis surrounding the neoplastic cell nests, (B) Dense eosinophilic hyaline material and necrotic keratin debris vaguely resembled. The neoplastic cells are diffuse and strongly positive for CK18; (C) Focal reactivity for β-HCG. (D) nuclear p63. (E) Expressed in 58% of tumour cells. (F) Ki-67 proliferation index is 77% [44]

3. POSITIVE DIAGNOSIS

3.1 Circumstances of discovery

In our series, the most frequent circumstances for diagnosis of TTG were the appearance of metrorrhagia, which is the main revealing symptom, and/or disturbances in serum β-hCG levels during post-molar follow-up in half of our patients (50% of cases).

In 50% of cases, the diagnosis of TTG was made on anatomopathological evidence from a haemostasis hysterectomy specimen.

In no case was the diagnosis revealed by metastases.

These circumstances are also found in various African and Asian series [5], which may be attributed essentially, in underdeveloped countries, on the one hand to the large number of patients lost to follow-up after molar abortion, and only consulted at the stage of complications. On the other hand, the economic context and low income of patients prevent adequate biological monitoring.

In Europe and North America, on the other hand, asymptomatic forms predominate because the diagnosis is made early on the basis of a disturbed biological evolution [31].

3.2 Delay between causal pregnancy and onset of GTT:

In half the cases, the delay between molar abortion and diagnosis of TTG was between 3 and 6 months, with an average of 4 months.

This is in line with the average delay of six months found in the literature [5, 44].

This justifies the need for intensive monitoring of patients for 12 months following molar abortion, the risk being much lower after 12 months [31, 5].

This monitoring should be based essentially on repeated measurements of serum β-hCG levels and on the search for metrorrhagia following a molar abortion [5, 44].

Table 6: Time between molar pregnancy and diagnosis of TTG

Region	Time between molar abortion and diagnosis of TTG
Senegal [7, 35]	7 months
Norway [45]	4 months
China [46]	6 months
France [31]	6 months

The occurrence of TTG after spontaneous miscarriage, extra uterine pregnancy or normal childbirth is extremely low, around 1/40000. This rarity excludes biological monitoring of normal pregnancies [31] (Table 6).

3.3 Diagnostic criteria:

The diagnostic criteria used are those proposed in 2000 by FIGO (FIGO, 2000) and are based on a consensus of experts [47].

For the patients in our series, the diagnosis of TTG was made on the basis of either:

- Biological disturbances in ß HCG levels following mole.
- Histological diagnosis.

We note that our diagnosis was justified and complied with the standards in all cases, which is in line with the figure in a FIGO update published in 2007 on compliance with the diagnostic criteria [44].

In this review, the main justifications for early treatment were the histological diagnosis of invasive mole and the presence of pulmonary or hepatic metastases in the context of mole [44].

In their analysis, they concluded that compliance with the FIGO diagnostic criteria and adaptation of chemotherapy to the FIGO stage-score made it possible to avoid over- or under-treatment of gestational trophoblastic tumours [44].

4. ASSESSMENT OF EXTENSION

+ Extension work-up to be carried out following diagnosis of GTT:

✓ For the Canadian Society of Obstetricians and Gynaecologists:

- If the chest X-ray is clear, a presumptive diagnosis of a non-metastatic tumour is made [44].
- In the presence of pulmonary metastases, CT scans of the brain and abdomen are indicated [48].
- In the absence of lung metastases on lung CT, the SCGO finds that no further investigation is necessary, as the risk of extra-lung metastases is very low (<1%) [48].
- In the presence of gastrointestinal bleeding, upper and lower gastrointestinal endoscopy is indicated. In the presence of haematuria, IVU and cystoscopy are indicated [48].

In practice, this assessment makes it possible to define the anatomical stage, calculate the score and classify patients according to the different scores.

✓ FIGO (FIGO and IGCS, 2006) recommends the following assessment:

- A chest X-ray.
- Cerebral MRI or, failing that, cerebral CT scan, in the case of identified or unidentified pulmonary metastases.
- An abdominal CT scan if liver metastases are suspected, and a full-body CT scan if lung metastases are detected on the chest X-ray.
- MRI if necessary, depending on the clinical situation (if other metastases are suspected).

✓ For the CNGOF 2010:

Once the diagnosis of GTT has been made, it is recommended that the extent of the disease be assessed, as this determines the prognosis (FIGO score, 2000):

- Local extension: an endovaginal pelvic ultrasound scan is recommended, if possible accompanied by a colour Doppler;
- Locoregional extension: pelvic MRI is recommended;
- Remote extension :
  - Search for pulmonary metastases by thoracic CT scan. If metastases are found, a chest X- ray is recommended to count and measure them in order to establish the FIGO 2000 score,
  - Search for liver metastases by abdominal CT scan and for brain metastases by brain MRI or, failing that, CT scan, whether or not lung metastases have been identified (professional agreement).

All our patients underwent pelvic ultrasound + Doppler, lung X-ray, and abdomino-pelvic and thoracic CT scans as part of the extension work-up.

Cerebral CT was requested in 4 patients, while pelvic MRI was requested in 2 patients.

5. METASTATIC CASES

For metastatic cases, our study showed that 40% of cases h a d metastases at different sites. This is the highest percentage compared with other studies conducted worldwide (Table 7). However, our study is fully in line with the literature concerning the most frequent site of metastatic localization, with 40% of patients with metastases presenting a pulmonary

localization in 1st rank (Table 8). However, liver metastases are the 2nd most common site, representing a frequency of 10%.

Unlike to studies, no of our patients presented cerebral or vaginal metastases (Table 8).

Table 7: Percentage of metastatic forms

Country	Frequency of metastatic forms
Senegal [7, 35]	38%
Norway [45]	31%
France [48]	8%
Rabat [31, 19]	14.5%
Our series	40%

Table 8: Percentage of different metastatic sites

Country	Lung	Liver	Vagina	Brain	Other
Senegal [7, 35]	70%	5%	25%	18%	5%
Norway [45]	77%	6%	-	12%	3%
France [48]	80%	10%	30%	20%	20%
Rabat [31, 19]	65%	12%	35%	-	-
Our series	40%	10%	-	-	-

6. PROGNOSIS SCORE

The score adopted in our training is that of FIGO. It was assessed in all our patients, with 60% (6 patients) having a low-risk score. ≤6 and in 40% (4 patients) a high-risk score ≥7.

7. THERAPEUTIC METHODS

7.1 Chemotherapy

The first chemotherapies recognised as effective in GTT were methotrexate and actinomycin D [49] used as monotherapy.

Since then, several polychemotherapies have been developed based on methotrexate, actinomycin D, etoposide, cisplatin, cyclophosphamide, vincristine and bleomycin [49].

A pre-treatment workup is routinely performed [49]:

- ✓ Full gynaecological and clinical examination
- ✓ A complete blood count,
- ✓ A plasma ionogram with creatinemia,
- ✓ A liver test with bilirubinemia.
- ✓ An assay of plasma β hCG and free B subunit.
- ✓ An extension assessment.
- ✓ Examination required to prescribe contraception.

Since the development of chemotherapy in the treatment of GTT, the cure rate has risen steadily, and now concerns virtually all patients.

Methotrexate as mono-chemotherapy is the first-line treatment for low-risk forms (FIGO score ≤6) [49].

Methotrexate is administered in the oncology department according to 2 protocols:

- MTX (1mg/kg IM on days 1, 3, 5 and 7) alternating with folic acid (failing this, folinic acid) at a dose of 0.1mg/kg/d on days 2, 4, 6 and 8. Every 14 days until β hCG levels are negative, followed by consolidation with two courses of the same treatment regimen.

Weekly MTX: 30 to 50mg/m2 IM, administered once a week until β hCG normalises, adding 2 courses 3 after negativation.

However, the addition of folic acid to methotrexate reduces the number of courses required to induce a complete response compared with methotrexate alone [49].

Our study found a complete remission rate in low-risk patients of 90%, with only one case of relapse on MTX (the case of IPTT) for which second-line CMT was indicated, which is in line with the data in the literature [50, 51].

In the event of failure of these protocols, all the protocols used for catch-up resulted in complete remission. In most studies, this involved polychemotherapy or actinomycin alone, which resulted in a complete response in 91/92 patients after failure of methotrexate alone, but another study reported a less clear-cut efficacy: only 6 complete responses in 15 patients [49].

Methotrexate has also been used in high-risk GTT; in 1987, Lurain explained that the factors responsible for treatment failures are the lack of appropriate initial aggressive therapy [49]. From 1962 to 1985, a series of 28 women from the John Brewer Trophoblastic Disease Centre died of a high-risk trophoblastic tumour treated with methotrexate [49].

At that time, high-risk patients treated with polychemotherapy had a survival rate of 63%, compared

with 30% for those treated with methotrexate, confirming that methotrexate should not be used alone in high-risk cases.

It is recognised that high-risk trophoblastic tumours (score ≥7) require polychemotherapy [49].

In the literature since 1979, EMA-CO has been the reference treatment for high-risk GTT at Charing Cross Hospital. In 2002, Lurain *et al*., listed the benefits of EMA-CO: better response rate, better long-term survival, minimal short- and long-term toxicity [49].

The remission rates were 73% and 95% respectively for Escobar and Bolis *et al*., [49, 52]. In our series, all high-risk GTT received EMA-based polychemotherapy CO.

In parallel with the data in the literature, our study found, for the following category of patients

In high-risk patients, the response rate to multi-drug therapy was 80%.

7.2 Surgery:

Today, the excellent chemosensitivity of these tumours reduces the need for mutilating surgery, especially in young women.

This was the case in our series, where surgery was only used for haemostatic purposes. However, there are still some indications for surgery [53].

In our series, 5 patients had benefited hysterectomy hysterectomy à hysterectomy for haemostatic purposes for non-dissipatable metrorrhagia. No surgery for metastatic sites was performed.

7.3 Radiotherapy

It still has a limited place in the management of GTT, especially as a palliative treatment for metastatic cases [49].

None of the patients in our series underwent radiotherapy.

7.4 Embolisation

The hypervascular and friable nature of GTT puts the patient at risk of significant haemorrhage [54]. Vaginal haemorrhage in particular can be a difficult circumstance to control in the management of these patients.

Packing and surgery, such as hysterectomy or uterine artery ligation, have long been the treatment of choice for controlling haemorrhage [55, 56].

A recent 2017 study by Wang in China [57] confirms the evidence reported in the literature; EDC can effectively control GTT bleeding leading patients to have a better response to subsequent systemic chemotherapy after successful EDC, although bleeding can recur in the presence of AVMs and early [58].

However, Carlini *et al*., [59] reported the case of a patient with negative βHCG levels after arterial embolisation alone without the use of secondary chemotherapy.

In our series, no patient benefited from this therapeutic procedure.

8. MONITORING

✓ **Clinical:** Systematic gynaecological examination enables the evolution of vaginal localisations to be monitored and, in some cases, the regression of uterine volume to be assessed.

✓ **Biological:** Monitoring after chemotherapy treatment, according to the consensus of the French National College of Gynaeco-Obstetricians 2010 (CNGOF), is based on repeated measurements of total serum β-hCG at the following intervals [47]:

- Once a week for the duration of the chemotherapy and the following 8 weeks.
- Every 15 days for the following 8 weeks.
- Then every month for up to 12 months in the case of low-risk GTT and up to 18 months in the case of high-risk GTT.
- The team at Charing Cross Hospital suggests follow-up based exclusively on monitoring urinary β hCG levels beyond the 6th month of follow-up [60].
- The first year: weekly monitoring of serum and urinary total β hCG levels for 6 weeks, then every 15 days until 6 months after treatment, then monitoring of urinary levels only every 15 days until 1 year after treatment.
- Monitoring of urinary β-hCG levels every month for the second year.
- Monitoring of urinary β-hCG levels every 2 months for the third year.
- Monitoring of urinary β-hCG levels every 3 months for the fourth year.
- Monitoring of urinary β-hCG levels every 4 months for the fifth year.
- Finally, urinary β-hCG levels are monitored every 6 months for the rest of the patient's life.
- Beyond the fifth year.

In our department we have adopted the French recommendations (CNGOF).

✓ Radiological: a pelvic and endovaginal ultrasound scan is performed after β hCG negativation, and then three, six and 12 months later.

An imaging study covering all the pathological sites from the initial work-up is carried out two weeks after the β hCG levels have returned to normal. This may reveal the persistence of residual masses. These masses

may regress spontaneously and should not undergo surgery, as a negative β hCG signal indicates a cure [61].

In our study, we found that the majority of patients who were monitored complied with the monitoring schedule.

And all patients were systematically put on oral contraception during chemotherapy and 1 year after stopping treatment.

9. FORECAST

9.1 Mortality

The prognosis of GTT improved markedly after the introduction of chemotherapy [62]. In our study, no deaths were reported.

A recent cohort study (2015), carried out at the French centre for gestational trophoblastic diseases on 974 patients followed for GTT, over a period of 15 years, concludes that FIGO score ≥13 of GTT is becoming a consensus criterion for increased risk of death, particularly early death. The 5-year mortality rate was 52% in the 29 patients with GTT with a FIGO score ≥13, 6 of whom died within 4 weeks of starting chemotherapy. Low-dose etoposide and cisplatin induction chemotherapy have recently been shown to reduce the rate of early death [63].

9.2 Morbidity

In our series, 2 patients experienced side effects of chemotherapy, such as vomiting, mucositis and febrile neutopenia.

- In the short term, cytotoxic drugs can have a variety of adverse effects ranging from simple inflammation of the mucous membranes, stomatitis, gastrointestinal disorders [64], to mortality.
- In the long term, the appearance of secondary tumours is increased, especially in the case of myeloid leukaemia, colon cancer, melanoma and breast tumours, with an average delay varying between 5 and 25 years [62]. Etoposide essentially increases the risk of secondary cancer [62], but these data have not yet been confirmed.

Gadducci's team in Italy (2015), reports an increased risk of myeloid leukaemia in patients who have received chemotherapy, mainly related to etoposide accumulation [65]. In our series, no cases of secondary tumour were found.

10. FERTILITY AND OBSTETRICAL OUTCOME:

Patients treated for TTG are generally young, which is why it is so important to preserve the possibility of pregnancy as far as possible.

Pregnancy is permitted one year after the end of treatment to allow correct monitoring of β-hCG levels and avoid any teratogenic effects secondary to chemotherapy [31].

However, if a pregnancy occurs within this time period, the termination does not have to be proposed but the pregnancy closely monitored [31].

The obstetrical future after TTG was well studied, the New England trophoblast disease centre published a review of the literature, collecting 1291 patients followed for pregnancy after chemotherapy, more than 77% of pregnancies resulted in the birth of a normal child, spontaneous abortions occurred in 13% of cases, congenital malformation in 2 to 3% of cases, which does not differ from the general population [31].

In our series, only one patient became pregnant 2 years after the end of surveillance, and her pregnancy and delivery proceeded normally without maternal or foetal complications.

V. CONCLUSION

TTGs are rare tumours with an excellent prognosis that require treatment in a competent and experienced department, so as not to compromise patients' chances of recovery and to preserve fertility.

Our work is a retrospective descriptive and analytical study of 10 cases of TTG collected in our institution over a period of 08 years:

- The risk factors for the majority of our patients were age, low socio-economic status and a history of molar pregnancy.
- Ultrasound plays an important role in diagnosis.
- Biology is of indisputable interest in making the diagnosis.
- Extensive work-up is essential, even in the absence of clinical signs.
- Delayed diagnosis accounts for a significant percentage of metastatic forms.

Nevertheless, the majority of patients had a favourable outcome, with complete recovery without sequelae, thanks to the integration of the new treatment methods.

In fact, the creation of a reference centre for trophoblastic diseases in our country, as in France and the United Kingdom, to advise medical teams faced with this disease, is not simply an additional asset but an essential condition for better management. The discussion of a prophylaxis strategy similar to that used in other high-prevalence countries therefore seems very reasonable.

BIBLIOGRAPHY

1. Tse, K. Y., Chan, K. K., Tam, K. F., & Ngan, H. Y. (2009). Gestational trophoblastic disease. *Obstetrics, Gynaecology & Reproductive*

Medicine, *19*(4), 89-97.
2. Dreyfus, M., Tissier, I., & Philippe, E. (2000). Les maladies trophoblastiques gestationnelles. *J Gynecol Obstet Biol Reprod*, *29*, 125-130.
3. Shi, Y. F., Li, J. Q., Zheng, W., Chen, X. J., Qiao, Y. H., Hao, M., ... & Zheng, X. (2005). Survey of gestational trophoblastic disease incidence among 3.6 million pregnancies in China. *Zhonghua fu chan ke za zhi*, *40*(2), 76-78.
4. Ben Zineb, N., Mourali, M., & Boussen, H. (2003). Rapport national présenté au 5ème congrés magrebin de gynécologie obstétrique. Casablanca.
5. Cisse CT, Lo N, Moreau JC, Fall-Gaye C, Mendez V, Diadhiou F. Choriocarcinoma in Senegal: epidemiology, prognosis and prevention. Gynécologie Obstétrique Fertil. 2002;30(11):826-869.
6. Ngan HY, Chan KK, Tam K-F. Gestational trophoblastic disease. Curr Obstet Gynaecol. 2006;16(2):93-99.
7. Bracken MB. Incidence and aetiology of hydatidiform mole: an epidemiological review. Bjog Int J Obstet Gynaecol. 1987;94(12):1123-1135.
8. Smith HO, Qualls CR, Prairie BA, Padilla LA, Rayburn WF, Key CR. Trends in gestational choriocarcinoma: a 27-year perspective. Obstet Gynecol. 2003;102(5):978-987.
9. Dessau R, Rustin GJS, Dent J, Paradinas FJ, Bagshawe KD. Surgery and chemotherapy in the management of placental site tumor. Gynecol Oncol. 1990;39(1):56-59.
10. Boutayeb Y, Ederdoui M, Setouani A; Influence on trophoblastic disease, J; Gynecol. Obstet. Biol. Reprot, 1982; 11, pages 78-80
11. Dawalibi J, Dufour P, Gaubert P, Occeli B, Block S, Lesoin A. Postpartum metastatic choriocarcinoma. A propos d'un cas: Revue de littérature. Rev Fr Gynécologie Obstétrique. 1997;92(3):191-198.
12. Korbel M, Sufliarsky J, Danihel L, Vojtassak J, Niznanska Z. Results of gestational trophoblastic neoplasia treatment in the Slovak Republic in the years from 1993 to 2012. Ceska Gynekol. 2016;81(1):6-13.
13. Denis V, Lyon Reference Centre for Trophoblastic Diseases. www.molechorio.com
14. Seckl, M. J., Fisher, R. A., Salerno, G., Rees, H., Paradinas, F. J., Foskett, M., & Newlands, E. S. (2000). Choriocarcinoma and partial hydatidiform moles. *The Lancet*, *356*(9223), 36-39.
15. Gerulat AH. Pregnant trophoblastic disease. Dir Clin Society of Obstetricians and Gynaecologists Can. 2002; 24.
16. Daniel Evain-Brion; Hormones placentaires humaines; Nutrition clinique et métabolisme; volume 16; Issue 3; September 2002; Pages 206-209.
17. Ming Shih, Ph.D, and Robert J. Kurman, M.D; The pathology of intermediate trophoblastic tumor and tumor-like lesions; International journal of gynecological pathology; 2001; 20; 31-47.
18. Soper JT. Staging and evaluation of gestational trophoblastic disease. Clin Obstet Gynecol. 2003; 46(3): 570-578.
19. Golfier, F., Raudrant, D., Frappart, L., Mathian, B., Guastalla, J. P., Trillet-Lenoir, V., ... & Schott, A. M. (2007). First epidemiological data from the French trophoblastic disease reference center. *American journal of obstetrics and gynecology*, *196*(2), 172-e1.
20. Sasaki K, Hata H, Nakano R. ABO blood group in patients with mali-gnant trophoblastic diseases. Gynecol Obstret Invest 1985; 20: 23-26.
21. Parazzini, F., La Vecchia, C., Franceschi, S., Pampallona, S., Decarli, A., Mangili, G., & Belloni, C. (1985). ABO blood-groups and the risk of gestational trophoblastic disease. *Tumori Journal*, *71*(2), 123-126.
22. Mohammad, J. R., Abedi, P., & Tadayon, N. M. (2010). The gestational trophoblastic diseases: a ten year retrospective study. *Int J Fertil Steril*, *4*(1).
23. The VIII th world Congress on gestational trophoblastic diseases. Nov 3-6, 1996, Seoul, Korea. International journal of gynecology & obstetrics, (1998) 60(suppl.no.1) S129-S136.
24. Berkowitz, R. S., & Goldstein, D. P. (2009). Molar pregnancy. *New England journal of medicine*, *360*(16), 1639-1645.
25. Hertig, A. T. (1956). Tumors of the female sex organs. Part 1: Hydatidiform mole and choriocarcinoma. *Atlas Tumor Pathol*, 1956, Section-IX.
26. Palmer, J. R. (1994). Advances in the epidemiology of gestational trophoblastic disease. *The Journal of reproductive medicine*, *39*(3), 155-162.
27. Parker, V. L., & Tidy, J. A. (2017). Current management of gestational trophoblastic disease. *Obstetrics, Gynaecology & Reproductive Medicine*, *27*(11), 338-345.
28. Stone, M., Dent, J., Kardana, A., & Bagshawe, K. D. (1976). Relationship of oral contraception to development of trophoblastic tumour after evacuation of a hydatidiform mole. *BJOG: An International Journal of Obstetrics & Gynaecology*, *83*(12), 913-916.
29. Palmer, J. R., Driscoll, S. G., Rosenberg, L., Berkowitz, R. S., Lurain, J. R., Soper, J., ... & Rao, R. S. (1999). Oral contraceptive use and risk of gestational trophoblastic tumors. *Journal of the National Cancer Institute*, *91*(7), 635-640.
30. Vuong, P. N., Guillet, J. L., Houissa-Vuong, S., Lhomme, C., Proust, A., & Cristalli, B. (2000). Pathology of gestational trophoblastic tumors. *Gynecologie, Obstetrique & Fertilite*, *28*(12), 913-926.
31. Golfier, F., Raudrant, D., Frappart, L., Guastalla, J. P., Trillet-Lenoir, V., & Mathian, B. (2003). Les môles hydatiformes et les tumeurs trophoblastiques: conduite à tenir pratique. *Mises à jour en gynécologie et obstétrique*, 53-99.
32. Dilbert, N., Drefus, M., Tissier, I., & Philippe, E.

(2006). Prise en charge des tumeurs trophoblastiques. *J. Gyneco. Obstet. Reprod*, *14*, 140-163.
33. Benirschke, K., & Kaufmann, P. (2000). Pathology of the human placenta. New York: Springer; 2000.
34. Cheung ANY. Pathology of gestational trophoblastic diseases. Best Pract Res Clin Obstet Gynaecol 2003; 17: 849-68.
35. Aonahata M, Masuzawa Y, Tsutsui Y. A case of intraplacental choriocarcinoma associated with placental hemangioma. Pathol Int 1998; 48: 897-901.
36. Barghorn A, Bannwart F, Stallmach T. Incidental choriocarcinoma confined to a near-term placenta. Virchow Arch 1998; 433: 89-91.
37. Jacques SM, Qureshi F, Doss BJ. Intraplacental choriocarcinoma associated with viable pregnancy: pathologic features and implications for the mother and infant. Pediatric Develop Pathol 1998; 1: 380-7.
38. Allias F, Bolze PA, Gaillot-Durand L, Devouassoux-Shisheboran M; Gestational trophoblastic disease network. Gestational trophoblastic disease. Annales de pathologie. Pages: 47-434. Nov 2014.
39. Berger G, Verbaere J, Feroldi J. Placental site trophoblastic tumor of the uterus: an ultrastructural and immunohistochemical study. Ultrastruct Pathol, 1994: 6: 319-329.
40. Eckstein RP, Paradinas FJ, Bagshawe KD. Placental site trophoblastic tumour (trophoblastic pseudotumour): A study of four cases requiring hysterectomy including one fatal case. Histopathology, 1982, 6: 211- 226.
41. Feltmate F, Genest DR, Wise L, Bernstein MR, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumor: A 17-year experience at the New England Trophoblastic Disease Centre. GynecolOncol, 2001, 82: 415-419.
42. Finkler NJ, Berkowitz RS, Driscoll SG, Goldstein DP, Bernstein MR. Clinical experience with placental site trophoblastic tumors at the New England Trophoblastic Disease Center. Obestet Gynecol, 1988, 71: 854-857.
43. Golfier, F., Labrousse, C., & Frappart, L. Evaluation of the management of gestational trophoblastic tumours registered at the Lyon reference centre for trophoblastic diseases from 1999 to 2005.
44. Bjørge T, Abeler VM, Sundfør K, Tropé CG, Kaern J. Gestational Trophoblastic Tumors in Norway, 1968-1997: Patient Characteristics, Treatment, and Prognosis. Gynecol Oncol. 2002;87(1):71-76.
45. HextanY, Ngan S: Gestational trophoblastic disease Current Obstetrics & Gynaecology (2003) 13, 95-101.
46. CNGOF; Recommandation de Bonne pratique; Maladies trophoblastiques gestationnelles; April 2010.
47. Ben Hazim O, Les tumeurs trophoblastiques gestationnelles à propos de 118 cas, Thèse pour l'obtention du Doctorat en médecine, Rabat 2012.
Gynaecology Obstetrics & Fertility 2007.
48. Inaguma S1, Wang Z, Lasota J, Sarlomo-Rikala M, McCue PA, Ikeda H, Miettinen M. Comprehensive Immunohistochemical Study of Programmed Cell Death Ligand 1 (PD-L1): Analysis in 5536 Cases Revealed Consistent Expression in Trophoblastic Tumors. May 2016
49. Schorge JO, Lea JS, Farrar DF, King MR, Coleman RL, Miller DS. Management of low-risk gestational trophoblastic neoplasia in indigent women. J Reprod Med. 2003; 48(10): 780-784.
50. Chan KK, Huang Y, Tam KF, Tse KY, Ngan HY. Single-dose methotrexate regimen in the treatment of low-risk gestational trophoblastic neoplasia. Am J Obstet Gynecol. 2006; 195(5): 1282-1286.
51. Korbe M, Sufliarsky J, Danihel L, Vojtassak J, Niznanska Z. [Results of gestational trophoblastic neoplasia treatment in the Slovak Republic in the years from 1993 to 2012] Jan 2016.
52. Phillipe E: Gestational trophoblastic diseases. J.rerod .med 1984.29:813-820.
53. Method MW, Hirschfield M, Averette HE. Angiographic-guided embolization of metastatic invasive mole. Gynecol Oncol. 1996;61(3):442-445.
54. Chattopadhyay SK, Roy BD, Edrees YB. Surgical control of obstetric hemorrhage: hypogastric artery ligation or hysterectomy? Int J Gynecol Obstet. 1990;32(4):345-351.
55. Paraskevaides E, Noelke L, Afrasiabi M. Internal iliac artery ligation (IIAL) in obstetrics and gynaecology. Eur J Obstet Gynecol Reprod Biol. 1993;52(1):73-75.
56. Wang, Z., Li, X., Pan, J., Chen, J., Shi, H., Zhang, X., ... & Xiang, Y. (2017). Bleeding from gestational trophoblastic neoplasia: embolotherapy efficacy and tumour response to chemotherapy. *Clinical Radiology*, *72*(11), 992-e7.
57. Maleux, G., Timmerman, D., Heye, S., & Wilms, G. (2006). Acquired uterine vascular malformations: radiological and clinical outcome after transcatheter embolotherapy. *European radiology*, *16*(2), 299-306.
58. Carlini, L., Villa, A., Busci, L., Trezzi, G., Agazzi, R., & Frigerio, L. (2006). Selective uterine artery embolization: a new therapeutic approach in a patient with low-risk gestational trophoblastic disease. *American Journal of Obstetrics & Gynecology*, *195*(1), 314-315.
59. Seckl, M. J. (2009). Investigation and treatment of patients with persistent gestationaltrophoblastic disease and gestational trophoblastic tumours/ neoplasia inthe United Kingdom: In gestational trophoblastic disease 3rd edition by Hancok B. W, Seckl M. J., Berkowitz R. S., Cole L. A.; 2009bis; pages: 343-365.
60. Noal, S., Joly, F., & Leblanc, E. (2010). Management of a gestational trophoblastic tumour.
61. Golfier, F., Raudrant, D., Frappart, L., Guastalla, J P., Trilletlenoir, V., Mathian, B., Seckl, M. J., Hajri, T., Schott, A. M. (2003). Collège national des

gynécologues et obstétriciens français Les môles hydatiformes et les tumeurs trophoblastiques: conduite à tenir pratique. Paris.

62. Bolze, P. A., Riedl, C., Massardier, J., Lotz, J. P., You, B., Schott, A. M., ... & Golfier, F. (2016). Mortality rate of gestational trophoblastic neoplasia with a FIGO score of≥ 13. *American journal of obstetrics and gynecology*, *214*(3), 390-e1.
63. Aplin, J. D. (1991). Implantation, trophoblast differentiation and haemochorial placentation: mechanistic evidence in vivo and in vitro. *J Cell Sci*, 99, 681-692.
64. Strickland, S., & Richards W. G. (1992). Invasion of the trophoblasts. *Cell*, 71, 355-357.
65. Gadducci, A., Lanfredini, N., & Cosio, S. (2015). Reproductive outcomes after hydatiform mole and gestational trophoblastic neoplasia. *Gynecological endocrinology*, *31*(9), 673-678.