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Chemotherapy is not needed when complete evacuation of gestational choriocarcinoma leads to hCG normalization

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ABSTRACT

Background: The standard treatment for gestational choriocarcinoma is chemotherapy.
Objective: To describe the risk of recurrence with expectant management of gestational choriocarcinoma that has reached a normal human chorionic gonadotropin level after tumor removal without adjuvant chemotherapy.
Methods: A retrospective multicenter international cohort study was conducted from 1981 to 2017 involving 11 gestational trophoblastic disease reference centers with patient's follow-up extended until 2023. Clinical and biological data of included patients were extracted from each center's database. The inclusion criteria were i) histological diagnosis of gestational choriocarcinoma in any kind of placental tissue retrieved, ii) spontaneous normalization of human chorionic gonadotropin level following choriocarcinoma retrieval, iii) patient did not receive any oncological treatment for the choriocarcinoma, iv) and at least 6 months of follow-up after the first human chorionic gonadotropin level normalization.
Results: Among 80 patients with retrieved gestational choriocarcinoma and whose human chorionic gonadotropin level normalized without any other oncological therapy, none had a recurrence of choriocarcinoma after a median follow-up of 50 months. The median interval between choriocarcinoma excision and human chorionic gonadotropin level normalization was 48 days. The International Federation of Gynecology and Obstetrics/World Health Organization risk score was $\leq$6 in 93.7% of the cases.
Conclusions: This multicenter international study reports that selected patients with gestational choriocarcinoma managed in gestational trophoblastic disease reference centers did not experience any relapse when the initial tumor evacuation is followed by human chorionic gonadotropin level normalization without any additional treatment. Expectant management may be a safe approach for highly selected patients.

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1. Introduction

Gestational trophoblastic diseases (GTD) encompass, among others, premalignant complete and partial hydatidiform moles, and malignant lesions called gestational trophoblastic neoplasia (GTN), one of which is gestational choriocarcinoma (GCC). GCC is a rare and aggressive GTN subtype with a high metastatic potential. Although most GCC occur after a molar pregnancy, they can also be found after any other kind of pregnancy, i.e. ectopic pregnancy, miscarriage or term delivery. The incidence of GCC is estimated to be approximately 1:40,000–50,000 term pregnancies and 1:40 complete hydatidiform mole [1,2].

Standard treatment of GCC is chemotherapy, with a regimen based on the tumor's risk profile. An International Federation of Gynecology and Obstetrics (FIGO)/World Health Organization (WHO) scoring system based on eight prognostic factors has been established to evaluate the risk of resistance to single agent chemotherapy [3]. Low-risk tumors, i.e. with a FIGO/WHO risk score lower or equal to 6, are treated with single agent chemotherapy; whereas high-risk tumors, i.e. with a FIGO/WHO risk score higher than 6, are treated with multiagent chemotherapy [4]. Monitoring serum human chorionic gonadotropin (hCG) is used as a reliable tumor biomarker.

The early initiation of low-risk GTN adequate treatment is associated with a 5-year survival rate of 98% [5,6]. However, the histology of choriocarcinoma is predictive of a decreased effectiveness of first-line single agent treatments compared to post-mole GTN [7–9]. It has been suggested that patients with histopathological evidence of choriocarcinoma and a FIGO/WHO risk score of 5 or 6 may benefit from upfront multiagent chemotherapy in case of pre-treatment hCG level >150,000 mIU/mL or metastatic disease [10].

The diagnostic confirmation of GCC often requires expert histopathological review, which may delay the final pathological diagnosis. During this reviewing interval, hCG level can decline spontaneously and eventually normalize without additional therapy.

The objective of this international study conducted in GTD reference centers was to assess the recurrence rate of GCC after primary complete tumor removal followed by hCG normalization without adjuvant therapy.

2. Materials and methods

2.1. Study design

This retrospective multicenter international cohort study involved 11 GTD reference centers (Fig. 1) affiliated to the International Society for the Study of Trophoblastic Diseases (ISSTD) [11]. Patients treated between 1981 and 2017 were included. Clinical, biological and outcome data of included patients were extracted from each center's database. Follow-up was extended until April 2023.

Patients registered in trophoblastic diseases reference centers provided informed consent for anonymous data analysis and storage in local databases and informed consent was waived if deidentified and anonymized records were reviewed, with institutional review board approval or ethics committees of the respective participating centers approval where required (B322201214659).

2.2. Patients' enrollment

Patients were included in this study if they were diagnosed with GCC in any kind of pathology specimen: second/third trimester placenta, product of curettage, uterus, fallopian tube or metastasis resection. Ovarian choriocarcinomas were included only if molecular genotyping proved the gestational origin. Referent pathologists of each center have systematically reviewed all initial histological diagnoses. At least 1 normal serum hCG level following GCC removal without any additional treatment was necessary. Patients who received a single methotrexate injection for an initial context of a suspected ectopic pregnancy prior to the diagnosis of GCC were not excluded from the study. At least 6 months of follow-up at one of the reference centers after the first normalized hCG level was required.

Patients with a previous history of GCC cured by chemotherapy or patients with non-gestational choriocarcinoma were excluded.

Patients with metastatic disease were not excluded from the study.

2.3. Initial workup and management of gestational choriocarcinoma

Along with clinical history and physical examination, an initial imaging workup was performed at the time of GCC diagnosis for the anatomical staging. It was considered complete if it included imaging of all the following anatomical regions: pelvis (ultrasound or MRI), abdomen (CT scan or ultrasound), and chest (X-ray for FIGO score ± CT scan) imaging. Brain evaluation (CT scan or MRI) was performed selectively in women with suspected distant lesions.

The FIGO/WHO risk score was calculated for each patient, based on available data. For the item "antecedent pregnancy", in the absence of molecular genotyping, we considered either the current term pregnancy for intraplacental choriocarcinoma or the last known pregnancy. When the patient reported no previous pregnancy, we scored missed abortion by default.

For the item "interval from index pregnancy", we used the interval between last known pregnancy termination and the excision of choriocarcinoma.

We defined the first hCG value available as the item "pre-treatment hCG". Since the diagnosis of choriocarcinoma was not suspected at the time of placental removal in most cases, first hCG level was measured after tumor evacuation for 47.5% of patients (n = 38), which may have underestimated the FIGO/WHO risk score.

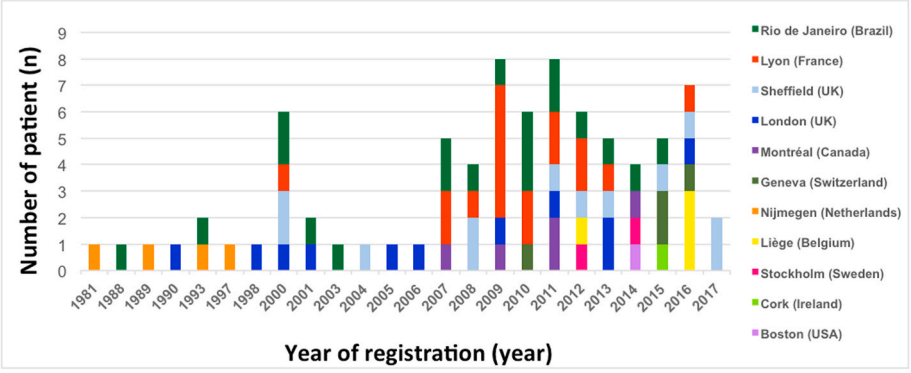

Fig. 1. Number and year of registration of choriocarcinoma cases followed by hCG normalization without chemotherapy in 11 Trophoblastic Reference Centers between 1981 and 2017.

For the item "largest tumor size", we used the size on gross pathological examination or tumor size on pelvic imaging when the pathological size was not available.

Disease recurrence was defined as rising hCG level after initial normalization confirmed after 2 weeks, in the absence of a new concomitant pregnancy [12].

Follow-up duration was calculated from the first normal serum hCG level to the last known hCG level.

3. Results

3.1. Center and patient characteristics

Eleven international trophoblastic diseases reference centers participated in this study: Rio de Janeiro-Brazil, Lyon-France, Sheffield-United Kingdom, London-United Kingdom, Montréal-Canada, Liège-Belgium, Nijmegen-Netherlands, Genève-Switzerland, Stockholm-Sweden, Boston-USA, and Cork-Ireland. Eighty patients with a pathological diagnosis of GCC and normalized hCG level were included. Fig. 1 shows the number of patients per center and the year of registration.

The diagnosis of GCC was made in 37.5% of women after uterine curettage (n = 30), in 26.3% after hysterectomy (n = 21), in 17.5% after delivery in the placenta (n = 14), in 15% in the fallopian tube (n = 12) and in 3.8% after metastatic resection (lung n = 2, kidney n = 1).

Two patients received two injections of 50 and 75 mg methotrexate respectively, for suspected ectopic pregnancy.

The clinical characteristics of patients according to the type of tumor excision are summarized in Table 1. Median age at the diagnosis was 34 years (range 17–54). The median time between the index pregnancy and the GCC diagnosis was 50 days (range 0–8030). The median first hCG level available was 1543 mIU/mL (range 0–223,591). The estimated tumor size was <3 cm for 81% of cases (n = 53/65), and 6% (n = 4/65) had a tumor size >5 cm. Tumor measurements were not available for 15 patients. The majority of patients had FIGO stage I (n = 62, 77.5%) or II (n = 14, 17.5%) disease. Five patients presented with metastatic lesions on imaging. In 2 patients, multiple lung lesions were described on chest CT scan performed after hysterectomy. One patient presented with a 4 cm cervical mass, after intraplacental choriocarcinoma excision. None of these 3 patients received chemotherapy since their hCG spontaneously fell rapidly after primary treatment. The remaining 2 patients with metastasis on imaging workup presented with a unique lung lesion corresponding to the excised GCC.

The FIGO/WHO risk scores ranged from 0 to 9 (Fig. 2): 0 in 3 patients (3.8%), 1 in 18 patients (22.5%), 2 in 33 patients (41.3%), 3 in 13 patients (16.3%), 4 in 1 patient (1.3%), 5 in 3 patients (3.8%), 6 in 4 patients (5%) and greater than 6 in 5 patients (6.3%).

Due to normalized hCG level at the time of the diagnosis, and in the absence of symptoms, imaging work-up was not always exhaustive. Imaging workup could be considered as complete in 70% (n = 56) of cases. For example, two patients with intraplacental choriocarcinoma had for example no imaging since the hCG level was already normalized at the time of diagnosis.

All cases were validated by an experienced team in gestational trophoblastic reference centers. Anatomopathological review, imaging work-up and scoring FIGO may lead to a time laps between surgery and treatment decision. Expectant management was decided in case of spontaneous normalization hCG in this interval. Omission of chemotherapy was never due to patient refusal or medical contraindication.

3.2. Recurrence rate

After a median follow-up of 50 months (range 6–411 months), none of the 80 patients experienced a GCC recurrence.

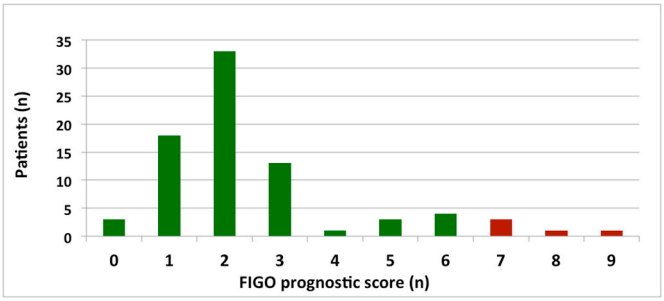

Fig. 2. Distribution of FIGO/WHO risk scores among the 80 patients included. In green, low-risk diseases with FIGO/WHO risk scores ≤6. In red, high-risk diseases with FIGO/WHO risk scores >6. This graph shows that majority of the patients included in this study had low-risk diseases. (For interpretation of the references to colour/colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Patients' characteristics according to the type of tumor excision.

	Uterine curettage	Hysterectomy	Term placenta	Fallopian tube	Metastasis resection	Total
	(n = 30)	(n = 21)	(n = 14)	(n = 12)	(n = 3)	(n = 80)
Age, median (year, range)	29.5	45	32	29	38.5	34 (17–54)
Antecedent pregnancy, n (%)[a]						
- Term delivery	9	10	14	0	1	35 (42.5)
- Miscarriage	10	5	0	0	1	16 (20)
- Ectopic pregnancy	0	0	0	12	0	12 (15)
- Hydatidiform mole	11	5	0	0	1	17 (21.2)
Interval from antecedent pregnancy and choriocarcinoma excision, median (day, range)[b]	53.5 (0–7348)	103 (0–8030)	0	0 (0–75)	740 (299-1181)	50 (0–8030)
Pre-excision hCG, median (mIU/mL, range)[c]	30,121 (2081–223,591)	13,494 (475-105,384)	NA	26,000 (307-222,486)	1221 (161-2282)	20,058 (161–223,591)
First post-excision, median (mIU/mL, range)[d]	443 (1–12,000)	550 (2–27,001)	2 (0–182)	528 (0–86,283)	1 (1–1)	182 (0–86,283)
Interval between excision and first normal serum hCG, median (day, range)[e]	57 (18–323)	55 (4–291)	42 (18–131)	47 (2–84)	28 (14–43)	48 (2–323)
Follow-up, median (month, range)	93 (6–329)	50 (8.5–411)	12 (6–139)	124 (11.5–209)	49 (39–87)	50 (6–411)

hCG, human Chorionic Gonadotropin; mIU/mL, milli International Units/milliliter; NA, not availableFigures

[a] missing data for 1 patient.
[b] missing data for 1 patient.
[c] missing data for 39 patients.
[d] missing data for 3 patients.
[e] missing data for 2 patients.

3.3. Characterization of hCG normalization

Pre-evacuation serum hCG levels were available in 52.5% cases (n = 42) with a median value of 20,058 mIU/mL (range 161–223,591). Median post-evacuation hCG level was 182 mIU/mL (range 0–86,283) and was measured after a median interval of 14 days (range 1 day–9 months).

The median interval between GCC primary removal and hCG normalization was 48 days (range 2–323). For 80% of the patients, hCG level had normalized within 3 months post-removal. Statistical analysis showed a correlation between first hCG post-evacuation level and time to normalization (Pearson's correlation coefficient r = 0.44; p < .0001). First hCG post-evacuation level accounts for 19.16% ($r^2 = 0.44^2 = 0.1936$) of total variability of necessary time to tumor marker normalization. High first hCG post-evacuation levels were therefore associated with a longer interval for hCG normalization (Fig. 3).

Among patients with intraplacental choriocarcinoma, 66% (n = 10/15) had normal values at their first hCG measurement.

4. Discussion

4.1. Principal findings

This multicentre international study shows no relapses of GCC after primary complete evacuation followed by hCG level normalization, without any additional treatment. These results highlight the opportunity to avoid chemotherapy exposure in highly selected patients.

4.2. Results in the context of published literature

The centralization of care in expert GTD centers has contributed to the improvement of GCC management in terms of treatment morbidity and mortality [6,13]. The process of histopathological review in these reference centers requires time and is associated with a delay between specimen evacuation, final diagnosis of GCC and treatment initiation. In several cases, hCG level normalizes within this time interval. Management of patients with normal tumor marker level and no evidence of residual disease after GCC removal is a particularly controversial issue.

Some published data leave open the question whether non-metastatic GCC should be managed with careful follow-up only or immediate chemotherapy [14–16]. Very limited data are available on the specific subset of patients with normalized hCG level after GCC evacuation. It is not clear if postponing chemotherapy is an undertreatment.

A retrospective study compared expectant management versus immediate chemotherapy for low-risk and non-metastatic GCC [15]. In this population, 55.3% of patients managed by surveillance only achieved complete sustained remission. Interestingly, among the 12 cases with normalized hCG level, no patient required chemotherapy, which is concordant with our observation.

Regarding the specific condition of intraplacental choriocarcinoma, a systematic review, considering 29 non-metastatic cases, showed no relapse in 24 out of 25 patients managed by surveillance only [14]. However, it is not clear which criteria were applied to decide between prophylactic chemotherapy or simple surveillance. The authors of this study recommend to avoid adjuvant chemotherapy in patients with non-metastatic disease and normal hCG level, but lifelong hCG monitoring is required.

The population of the present study is heterogeneous in terms of pregnancy gestational age (first, second or third trimester) and metastatic status. Moreover, 28% of patients were older than 40 years old, which is a known risk factor for resistance to monochemotherapy in the treatment of GCC.

The duration of post-normalized hCG monitoring is still debated after chemotherapy for GTN. Published data show that most recurrent GTN appear in the first year of follow-up, regardless of the FIGO/WHO score risk [17,18]. Recurrent GCC occurs usually within the 3 years [19]. The consensus is to follow-up patients for at least 1 year after cessation of therapy, though with some centers advocating up to 10 years of follow-up [17–20]. In the present study, the median follow-up was 4 years, which is in accordance with practice in most centers and allows the diagnosis of the vast majority of recurrences.

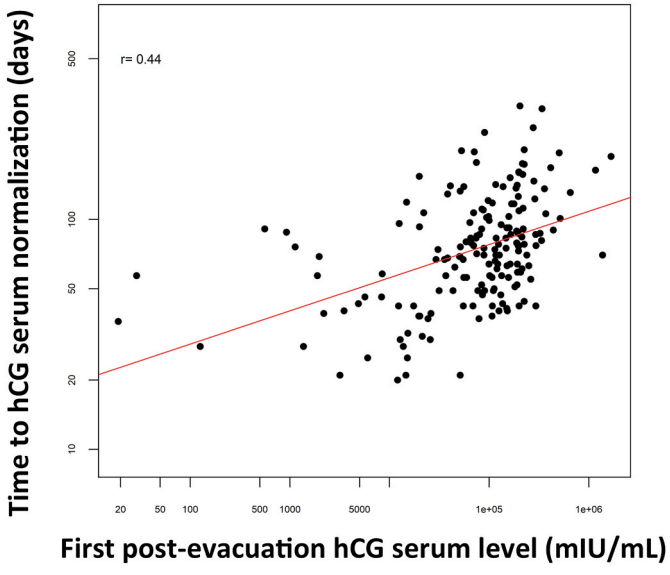

Fig. 3. Study of the correlation between the first post-evacuation hCG level and the time required to obtain normalization of hCG. This graph shows a correlation between first post-evacuation hCG level and time to normalization (Pearson's correlation coefficient r = 0.44; p < .0001).

4.3. Strengths and limitations

The strengths of this study are the multicentric international design and the involvement of recognized expert trophoblastic diseases centers with systematic histopathological review. This cohort of 80 patients is the largest cohort available in the literature in this very restricted subgroup of patients.

We also acknowledge some limitations, such as the retrospective design. FIGO scores were calculated thanks to available data, sometimes without knowing the index pregnancy, since genotyping is not routinely done. Our conclusions should therefore be interpreted with caution and the "surveillance only" decision must be validated in a multidisciplinary expert GTD center to avoid metastatic disease as a deleterious consequence of postponing chemotherapy.

4.4. Clinical and research implications

Our results highlight the consideration of an expectant approach in highly selected cases of GCC when the hCG level falls and eventually normalizes after complete tumor removal, especially in early stage low-risk disease. These results need to be validated in a larger and prospective study. In the future, it may change the FIGO recommendation to initiate chemotherapy in all cases of GCC histology. This management should always be validated by an experienced team in gestational trophoblastic reference centers.

5. Conclusions

This international multicenter study shows that patients with a primary diagnosis of GCC managed in GTD reference centers do not relapse when the initial tumor excision is followed by a normalization of hCG level without adjuvant treatment. These results, however, should be interpreted with some reservation as they only concern a selected cohort

of patients.

Conflict of interest

The authors report no conflict of interest.

Conflict of interest statement

The authors have no competing interests to declare with respect to this article.

CRediT authorship contribution statement

Pa Bolze: had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, Study concept and design, Formal analysis, interpretation of data, Drafting of the manuscript, Statistical analysis, Study supervision. **S. Schoenen:** had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, Formal analysis, interpretation of data, Drafting of the manuscript, Statistical analysis. **M. Margaillan:** Drafting of the manuscript, Statistical analysis. **A. Braga:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **P. Sauthier:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **K. Elias:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **M. Seckl:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **M. Winter:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **J. Coulter:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **C. Lok:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **U. Joneborg:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **M. Undurraga Malinverno:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **T. Hajri:** Statistical analysis, Administrative, technical, or material support. **J. Massardier:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **B. You:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **F. Golfier:** Acquisition of data, Critical revision of the manuscript for important intellectual content. **F. Goffin:** had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, Study concept and design, Formal analysis, interpretation of data, Drafting of the manuscript, Study supervision.

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