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When to stop human chorionic gonadotrophin (hCG) surveillance after treatment with chemotherapy for gestational trophoblastic neoplasia (GTN): A national analysis on over 4,000 patients☆

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HIGHLIGHTS

- Recurrence rate of 4.7% observed in this cohort of over 4000 patients with Gestational Trophoblastic Neoplasia.
- No relapses observed beyond seven years following treatment for GTN in this dataset.
- New national policy recommends patients now continue hCG screening for 10 years only.

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ABSTRACT

Objective. To determine the optimal duration of human chorionic gonadotrophin (hCG) surveillance following treatment for low and high risk gestational trophoblastic neoplasia (GTN) and establish whether the current surveillance protocol that recommends life-long hCG monitoring requires revision.

Methods. A population-based cohort study was undertaken using a national registry, comprising patients from both tertiary trophoblastic disease treatment units in the UK (London and Sheffield). All patients who received chemotherapy for low or high risk GTN in the UK between 1958 and 2014 in London and 1973 and 2015 in Sheffield (n = 4201) were included in the study. Patients with placental site trophoblastic tumours and epithelioid trophoblastic tumours were excluded due to their distinct clinical behavior, treatment and follow-up requirements. The risk of recurrence with time following completion of chemotherapy for low or high risk GTN was measured.

Results. The overall risk of relapse in this national cohort of 4201 patients was 4.7% (198/4201) with a median time to recurrence of 117.5 days (range 9 days to 6.54 years). The greatest risk of recurrence occurred in the first year after completing treatment for either low or high risk GTN measuring 72.7% (n = 112) or 86.4% (n = 38), respectively. The subsequent recurrence risk reduced over time with none observed beyond 7 years.

Conclusions. The absence of any recurrences beyond seven years following completion of chemotherapy for GTN indicates that the UK policy of life-long hCG surveillance is unnecessary. Our revised conservative protocol recommends stopping after 10 years.

1. Introduction

Gestational Trophoblastic Neoplasia (GTN) comprises a spectrum of malignant pregnancy-related tumours including invasive mole, choriocarcinoma and the extremely rare placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). More than 98% of cases are curable [1]. This is attributed to the highly chemotherapy-sensitive nature of most of these tumours, the ready availability of a biomarker for response to treatment (human chorionic gonadotrophin; hCG) and the centralised care of these patients into dedicated tertiary centers. Following the discovery of effective treatment for women with GTN in the late 1950s [2], a UK national register was established in 1973 [3]. All GTN patients who require

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chemotherapy have since been treated exclusively at one of two regional trophoblastic disease centres located in London and Sheffield. This has resulted in the largest database of patients with GTN worldwide [4] and enabled many subsequent improvements in disease outcome.

Apart from PSTT/ETT, the systemic treatment of GTN is guided by a scoring system to determine the risk of the disease becoming resistant to single agent chemotherapy with either methotrexate or actinomycin D. The first UK scoring system was devised by Bagshawe in the 1970s and stratified patients into three groups termed low, medium and high risk for resistance to methotrexate [5,6]. Patients scoring low risk received single agent chemotherapy whilst those scoring medium or high risk received different combination agent chemotherapy regimens. However, it became clear that 30% of patients within the medium risk group could be cured with single agent methotrexate [6] so these individuals were unnecessarily being exposed to more toxic combination agent treatment. Consequently, from 1990 onwards the low and medium risk groups were amalgamated to form a new low risk group recognising that all patients failing methotrexate could still be successfully treated with combination agent chemotherapy. The scoring system was further revised some years later into the International Federation of Gynaecology and Obstetrics 2000 (FIGO) scoring system (Table 1) [7]. A score of 0–6 indicates disease with a low risk (combined old low and medium risk groups) of resistance to single agent chemotherapy. In the UK these patients continue to be treated with methotrexate and folinic acid rescue (MTX/FA) as previously described [1]. Patients who develop resistance to MTX/FA, either during initial therapy or who subsequently relapse after entering an hCG remission, are successfully salvaged with subsequent lines of single or multi-agent treatment so that overall survival is virtually 100% [8–10]. Scores of 7 or more identify patients at high risk of resistance to single agent chemotherapy, and these women currently receive etoposide, methotrexate and actinomycin-D (EMA) alternating weekly with cyclophosphamide and vincristine (CO) [11] although in the past, patients in Sheffield had methotrexate, etoposide and actinomycin D (MEA) chemotherapy [11,12]. Survival following these treatments has been shown to be approximately 95% [13,14].

After completion of chemotherapy, patients undergo prolonged hCG monitoring with decreasing frequency, which in the UK eventually entails six monthly urine samples for life (Table 2) [1]. This has been done because of the uncertainty regarding when follow-up can be safely stopped [13,15] and to enable collection of long-term information regarding the health of women treated for GTN, including their subsequent fertility and cancer risks. However, such long-term follow-up has the potential to induce many years of on-going anxiety for the affected women and their families [16,17] and may now be unnecessary. Indeed, previous studies indicate that whilst there is an overall 4% risk of recurrence, 75% of these occur within the first year of follow-up [18]. Consequently, there is a need to re-evaluate whether life-long hCG monitoring is really necessary after treatment of either low or high risk GTN patients. To address this question we investigate the timing of relapses after GTN treatment.

Table 2
Current UK hCG surveillance protocol.

Duration following chemotherapy	Urine hCG	Serum hCG
1–6 weeks	Every week	Every week
2–6 months	Every 2 weeks	Every 2–4 weeks
7–12 months	Every 2 weeks	–
Year 2	Every 4 weeks	–
Year 3	Every 2–6 months	–
Year 4	Every 3–6 months	–
Year 5	Every 4–6 months	–
Year 6 onwards	Every 6 months	–

2. Methods

Hospital electronic databases were used to identify patients who received chemotherapy for GTN between 1958 and 2014 at Charing Cross Hospital (CXH; n = 3269) and between 1973 and 2015 at Weston Park Hospital (WPH; n = 932). Of the patients treated at CXH, 3045 had complete follow up data. Of the patients treated at WPH, complete follow up data was available for all those who relapsed (n = 37) and this cohort was utilized for validation purposes. Patients with a diagnosis of PSTT or ETT were excluded as the clinical behaviour and management of these GTN variants differ from low and high risk GTN [1,15,19–21]. The data presented includes only patients from the UK; international referrals were excluded.

Data was collected on the initial chemotherapy regimen administered and resistance events requiring a second line of treatment. Prior to 1990 at Charing Cross Hospital, patients were allocated to low, medium (hydroxyurea, methotrexate, 6-mercaptopurine, actinomycin-D, vincristine and cyclophosphamide or etoposide) or high risk chemotherapy regimens depending on their FIGO prognostic score [22]. After 1990, the medium risk category was abolished and these patients were subsequently managed according to the low risk protocol as previously published [8,9]. Approximately two-thirds of low risk patients will enter an hCG remission with MTX/FA alone, with the remainder requiring either actinomycin D and/or EMA/CO to achieve their first remission due to development of resistance or toxicity [8]. Similarly, whilst most high risk patients will enter remission with one combination agent therapy others may need one or two additional treatments before achieving a series of normal hCG levels [13,14].

To calculate the time to relapse we subtracted the date of relapse from the date of first hCG remission. The date of remission was defined as the end of chemotherapy treatment; in the UK this is 6 and 8 weeks after normalisation of hCG for low/high risk and ultra-high risk (FIGO score > 12) disease, respectively. The date of relapse was the date when first relapse chemotherapy was commenced.

Survival analysis by Cox regression was carried out in the R statistical programming environment (version 3.4.3) using the survival package.

This was a retrospective evaluation of one aspect of a NHS nationally commissioned (NHSE) specialised service. The study was approved by the institutional review board as a service evaluation at Charing Cross and was registered as a service evaluation with the Clinical Effectiveness Unit at Sheffield Teaching Hospitals NHS Foundation Trust. No patients

Table 1
International Federation of Gynecology and Obstetrics (2000) scoring system for gestational trophoblastic neoplasia, by prognostic factor [7]
A patient's score is calculated from the individual scores for the eight prognostic categories.

	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from antecedent pregnancy to chemotherapy (months)	<4	4–6	7–12	>12
hCG concentration	10^3	10^3–$<10^4$	10^4–10^5	$>10^5$
Number of metastases	0	1–4	5–8	>8
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal tract	Brain, liver
Largest tumour mass diameter (cm)	–	3–5	>5	–
Previous chemotherapy	–	–	Monotherapy	Combined therapy

were involved in establishing the research question or the outcome measures. There was no patient participation in either the design or implementation of this study. The results of this study will be disseminated to the relevant patient community.

3. Results

3.1. Overall recurrence rates following systemic therapy according to FIGO low vs high risk score

In this national cohort of 4201 GTN patients, 3507 (83.5%) received a low or medium risk chemotherapy and 694 (16.5%) a high risk regimen as first line therapy. Of these 4201 patients, 198 (4.7%) subsequently developed recurrent GTN.

In the CXH cohort for whom complete follow-up data were available for 3045 cases, overall 5.3% had a relapse recorded (n = 161 relapsed/3045 treated). Patients treated with the low and medium risk protocols combined had a significantly lower relapse rate compared to the high risk treatment group (total 4.7 vs 8.6% relapsed; hazard ratio 0.52, 95% confidence interval 0.36 to 0.74, $p < 0.001$). In agreement with data from CXH, the rate of relapse in the WPH cohort was significantly lower in patients treated with low/medium risk vs. high risk protocols (hazard ratio 0.19, 95% confidence interval 0.06 to 0.59, $p = 0.004$).

3.2. Trends in risk of recurrence relative to time from completion of treatment

Within the national cohort of 4201 patients, the median time to recurrence was 117.5 days (range of 9 days to 6.54 years). The absolute number of recurrences for each year following treatment in low/medium and high risk groups is shown in Table 3. In both groups, most relapses occurred within the first year of follow-up and there were no documented recurrences beyond seven years of completing first line treatment.

In agreement with our previously reported findings, the greatest risk of relapse is in the first year after treatment and generally falls thereafter [18]. S1 shows the risk of relapse according to years from completion of treatment for low and high risk groups.

3.3. Impact of cessation of medium risk chemotherapy regimens on risk of recurrence

The effect of a change in practice with the cessation of the medium risk chemotherapy regimen after 1990 was reviewed in the CXH cohort. Between 1958 and 1989, 13.8% (38/276) of patients relapsed following combination agent medium risk chemotherapy. After this protocol was eliminated in 1990 by combining the medium risk with low risk patients into a single, low risk group treated with MTX/FA, there was a significant drop in the risk of recurrence (3.4% recurred, 54/1574; hazard ratio 0.24, 95% confidence interval 0.16 to 0.36, $p < 0.001$). In contrast, there was no difference in the risk of relapse of low risk patients treated pre vs. post 1990 (4.2% vs 3.4%; hazard ratio 1.14, 95% confidence interval 0.3 to 1.80, $p = 0.56$).

Table 3
Recurrences according to prognostic risk treatment regimen and time from cessation of treatment.

	Low risk n = 154 (%) (includes former medium risk)	High risk n = 44 (%)
Year 1	112 (73)	38 (86)
Year 2	19 (12)	4 (9)
Year 3	17 (11)	0 (0)
Year 4	2 (1)	1 (2)
Year 5	1 (1)	0 (0)
Year 6	2 (1)	0 (0)
Year 7	1 (1)	1 (2)
>Year 7	0 (0)	0 (0)

4. Discussion

4.1. Principal findings

To our knowledge, this is the first time the optimal period of hCG surveillance after treatment for GTN has been explored and this national dataset is the largest of its kind internationally. We have established that among 4201 patients treated in the UK within the defined study period, no patients were diagnosed with recurrent disease beyond seven years of completion of treatment. This has significant implications for the current standard of care in the UK where patients undergo lifelong hCG surveillance after chemotherapy for GTN. Our results provide the first definitive evidence that life-long follow-up is unnecessary, an inefficient use of valuable resources and a potential source of inconvenience and significant anxiety for patients affected. An hCG surveillance period of ten years would satisfactorily identify all of the relapses in our study cohort as well as allowing for potential outliers that may have been missed in the present investigation.

4.2. Strengths and weaknesses

All patients treated with chemotherapy for GTN in the UK are managed by either Charing Cross Hospital or Weston Park Hospital. Thus, all the data was sourced from only two centres leaving very little potential for case ascertainment bias. Furthermore, all hCG measurements of patients in our study cohort were performed using the same optimised assays and central pathology review was carried out regardless of where samples were originally obtained.

While this study of 4201 patients is unique and represents the largest cohort internationally available, it was retrospective and therefore dependent on the accuracy of the information entered onto our electronic databases. We also acknowledge that changing chemotherapy and supportive treatments over time may influence the chemotherapy dose intensity of treatment delivered and hence the rate and timing of relapse.

4.3. Implications for clinicians and policy makers, unanswered questions and future research

In agreement with previous reports [18,23] our data demonstrate that the risk of recurrence is highest in the first year after treatment cessation and thereafter falls rapidly. It is for this reason that the current hCG surveillance schedule (Table 2) advises hCG monitoring with maximal intensity in the first year with subsequent decreasing frequency. The median time to recurrence was about 4 months (117.5 days) in our dataset. This differs slightly to the reported mean recurrence time of 6 months in Boston, 3 months at Duke and the median recurrence time of 6.5 months in Hong Kong [24–26]. The differences seen likely reflect the smaller size of the other studies that were conducted in centers where case ascertainment bias is a likely issue, in contrast to our large study in a national center not subjected to case ascertainment bias.

The recurrence risk drops off steeply after Year three (1:237 to 1:501) and it could be argued that the vast majority of recurrences would be captured if hCG surveillance were stopped at this point. Indeed, the NCCN guidelines for GTN recommend a surveillance schedule of monthly assays for just one year after treatment [27]. However, since late detection of recurrence likely increases the risk of failure to subsequently cure patients [1] the new UK policy will more conservatively continue monitoring up to 10 years for all low and high risk group patients. Since little is known about ultra-high risk patients and those with PSTT/ETT, these women will continue to be monitored for life at present.

The revised 10-year surveillance schedule was introduced in the UK in December 2018. This led to the immediate discontinuation of twice yearly hCG testing for 1240 patients from CXH and 266 from WPH, with significant associated financial savings. At a cost of £8 for each hCG assay and postage, this will result in a saving per annum of approximately £20,000 at CXH and £4,250 at WPH. Of the 1240 patients at CXH, approximately 200 had been undergoing hCG surveillance for over 40 years; stopping hCG testing at 10 years would have saved £96,000 for these patients alone.

The recommendation for a shorter hCG surveillance period will exclude selected patients who have received newer treatments such as high dose chemotherapy, immunotherapy or have a diagnosis of ultra-high risk GTN (defined as patients with a FIGO score ≥ 13 [28]), PSTT or ETT. For this small subset of patients, lifelong hCG surveillance at the current interval frequency remains recommended until sufficient data about their recurrence risk has been collected to review this duration.

4.4. Other findings

A subanalysis of this study examined the effect of the cessation of the medium risk chemotherapy regimen on the risk of recurrence. There was a significant decrease in recurrence risk for patients who would historically have been given low or medium risk treatment regimens when all these patients received the same (low risk) chemotherapy regimens after 1990. Recent discussion within the international community of healthcare professionals who manage GTN has raised the question of whether reintroduction of a medium risk treatment regimen would be beneficial. Our data suggests that the previously used medium risk treatment (hydroxyurea, methotrexate, 6-mercaptopurine, actinomycin-D, vincristine and cyclophosphamide or etoposide) does not reduce the recurrence rate and, if medium risk treatment were to be reconsidered, an alternative chemotherapy regimen would be required.

5. Conclusions

This national dataset with over 4000 patients clearly indicates that the duration of the current recommended UK hCG surveillance policy is unnecessary. This has led to the development and implementation of a revised national policy, whereby the majority of patients are no longer advised to continue hCG screening beyond 10 years of completion of treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.07.024.

Author contribution

Kirsty Balachandran collected and analysed the data from Charing Cross Hospital and wrote the manuscript. Abdulazeez Salawu collected and analysed the data from Weston Park Hospital and contributed to the manuscript. Ehsan Ghorani carried out statistical analysis and contributed to the manuscript. Baljeet Kaur and Neil J Sebire oversaw the histological review of patient pathology samples. Dee Short was responsible for managing and identifying relevant data from the Charing Cross hospital database. Barry Hancock is a previous Director of the Sheffield Trophoblastic Disease Centre and contributed to the manuscript. John Tidy is the Current Director of the Sheffield Trophoblastic Disease Centre and contributed to the manuscript. Kamaljit Singh helped with data identification and collection of the Sheffield patients. Richard Harvey provided analyses of human chorionic gonadotrophin results. Naveed Sarwar contributed to the analysis of the Charing Cross hospital data and to the manuscript. Matthew C Winter oversaw the analysis of the Weston Park Hospital data and contributed to the manuscript. Michael J Seckl oversaw the analysis of the Charing Cross Hospital data, contributed to the manuscript and is also responsible for the overall content and conduct of the study as the guarantor and controlled the decision to publish this study.

Declaration of Competing Interest

All authors have completed the ICMJE form for disclosure of potential conflicts of interests and declare there has been no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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