European Journal of Obstetrics and Gynecology 286 (2023) 76–84

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Full length article

Challenging gestational trophoblastic disease cases and mimics: An exemplar for the management of rare tumours

M. Hamid [a,1,3], C.M. Joyce [b,c,d,*,1,4], H.K. Carroll [a], C. Kenneally [e], S. Mulcahy [e], Mary-Kate O'Neill [e], J. Coulter [e], S. O'Reilly [a,f,2]

[a] Department of Medical Oncology, Cork University Hospital, Cork, Ireland
[b] Pregnancy Loss Research Group, Department of Obstetrics & Gynaecology, University College Cork, Cork, Ireland
[c] Department of Biochemistry and Cell Biology, University College Cork, Cork, Ireland
[d] Department of Clinical Biochemistry, Cork University Hospital, Cork, Ireland
[e] Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, Cork, Ireland
[f] Cancer Research @UCC, University College Cork, Cork, Ireland

ARTICLE INFO

Keywords:
Gestational Trophoblastic Disease
Rare Tumours
Molar Pregnancy
Ovarian Dysgerminoma
Choriocarcinoma
Case Report

ABSTRACT

Objective: Rare tumour management is challenging for clinicians as evidence bases are limited and clinical trials are difficult to conduct. It is even more difficult for patients where self-reliance alone is insufficient to overcome the challenges of navigating care which is often poorly evidence based. In Ireland, a national Gestational Trophoblastic Disease (GTD) service was established as one of 3 initiatives for rare tumours by the National Cancer Control Programme. The service has a national clinical lead, a dedicated supportive nursing service and a clinical biochemistry liaison team. This study sought to assess the impact of a GTD centre using national clinical guidelines and integrating and networking with European and International GTD groups on the clinical management of challenging GTD cases and to consider the application of this model of care to other rare tumour management.

Study Design: In this article, we analyse the impact of a national GTD service on five challenging cases, and review how the service affects patient management in this rare tumour type. These cases were selected from a cohort of patients who were voluntarily registered in the service based on the diagnostic management dilemma they posed.

Results: Case management was impacted by the identification of GTD mimics, the provision of lifesaving treatment of metastatic choriocarcinoma with brain metastasis, networking with international colleagues, the identification of early relapse, the use of genetics to differentiate treatment pathways and prognosis, and supportive supervision of treatment courses of up to 2 years of therapy in a cohort of patients starting or completing families.

Conclusion: The National GTD service could be an exemplar for the management of rare tumours (such as cholangiocarcinoma) in our jurisdiction which could benefit from a similar constellation of supports. Our study demonstrates the importance of a nominated national clinical lead, dedicated nurse navigator support, registration of cases and networking. The impact of our service would be greater if registration was mandatory rather than voluntary. Such a measure would also ensure equity of access for patients to the service, assist in quantifying the need for resourcing and facilitate research to improve outcomes.

Introduction

Rare cancers are defined as those with an annual incidence of <6 per 100,000 per year and account for 22% of all newly diagnosed cancers. [1–3] These rare cancers account for at least 5,200 annually diagnosed cancer cases in Ireland. Lack of information and guidelines on their

* Corresponding author.
E-mail address: carolinejoyce@ucc.ie (C.M. Joyce).
[1] M Hamid and CM Joyce contributed equally to this article and should be considered joint first authors.
[2] Orcid: 0000-0002-2887-7336.
[3] Orcid: 0000-0001-5809-9208.
[4] Orcid: 0000-0001-7231-8331.

https://doi.org/10.1016/j.ejogrb.2023.05.016
Received 6 March 2023; Received in revised form 5 May 2023; Accepted 12 May 2023
Available online 13 May 2023

management leads to more isolation and distress for patients and their families.[4] Challenges in the management of these rare cancers also includes their heterogeneity [5–8], and lack of level 1 evidence from clinical trials,[9] resulting in inadequate diagnosis and treatment.[10] Consequently, contemporaneous registry-based studies have documented poorer 5-year survival rates for rare cancers compared to common ones, and a failure for the former group to benefit from the gains in cancer survival that have occurred in recent decades. [11].

Recognition of the significance of rare cancers has led to several initiatives including; RARECARE – the project surveillance of rare cancers in Europe,[2] the establishment of European Reference Networks (ERNs),[12] in particular EUROCAN, the ERN for rare adult solid cancers, [13] and the International Rare Cancers Initiative.[14,15] These evolving international initiatives need to be integrated into care pathways for patients with rare cancers. One such rare tumour is Gestational Trophoblastic Disease (GTD) which arises from abnormal proliferation of trophoblastic cells in the placenta.[16] Hydatidiform mole (HM) or molar pregnancy is the most common pre-malignant type of GTD. HMs have two copies of the paternal genome and exist as partial or complete moles with the latter having a higher propensity for malignancy. [17,18] HM may be suspected on ultrasound and supported by elevated levels of human chorionic gonadotrophin (hCG), but diagnosis is made by histopathological examination of the evacuated products of conception (POC). At early HM presentation, diagnosis on morphology alone may be challenging due to GTD mimics and ancillary techniques (in-situ hybridisation, flow cytometry, molecular genotyping) are often required to aid diagnosis. [19–22] The pathogenesis of GTD is unique in that the maternal tumour arises from gestational tissue rather than maternal tissue.[23] The World Health Organisation recognises four malignant GTD disorders; invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT).[24] In Europe, the incidence of choriocarcinoma is 1 per 40,000 pregnancies [25] whereas PSTT/ETT are even rarer accounting for 0.2% of all GTD. [26] These malignancies can occur months or years after a pregnancy and are often detected based on obstetric history and raised human chorionic gonadotrophin (hCG) levels.[27] However, choriocarcinoma is very responsive to chemotherapy and even patients presenting with advanced disease can achieve cure rates approaching 100%.[17,26,28].

In Ireland, the National Cancer Control Programme has established national multidisciplinary teams for sarcoma, neuroendocrine cancers and for GTD management to assist treatment in 8 National Cancer Centres.[29] The national GTD centre based at Cork University Maternity Hospital was established in 2017 by the National Cancer Control Programme (NCCP) as a monitoring and advisory centre. National clinical guidelines for the management of GTD developed by the NCCP with multidisciplinary involvement from members of the GTD centre in Cork recommend registration of all affected women with a GTD centre as a minimum standard of care.[30] The national GTD centre has a clinical lead and is supported by clinical nurse specialists who operate to best practice guidelines [31] and organise regular hCG follow-up testing at local hospitals and contact patients with their hCG results. Patient participation and involvement is integrated through advisory board membership and integration of patient experience survey results. The role of the expert GTD centre in Ireland has not yet been quantified. In the present study we assessed the impact of this initiative and reflect on how learning points from these cases could extend to other rare tumours nationally.

Material and methods

Study Design:

Since its inception in 2017, the Irish national GTD centre has registered 748 GTD cases consisting of 10 women with gestational trophoblastic neoplasia (8 choriocarcinomas, 1 PSTT, I ETT). We performed a retrospective review of cases on the GTD registry and selected five illustrative cases treated at the GTD centre for review. In all cases presented, women provided informed consent in accordance with the Code of Ethics of the Declaration of Helsinki.

Inclusion criteria:

For this case series, cases were selected for review based on their clinical significance, the diagnostic and treatment dilemma that they posed such as life-threatening presentations, disease types mimicking trophoblastic disease and cases where the clinical course was not as anticipated. A unifying theme in these cases was the need for multidisciplinary discussion often with international collaborators and integration with nationally developed clinical GTD guidelines.[30] The intent of the selected cases was to demonstrate the pivotal role of the national GTD centre in the management of a rare tumour.

Analytical methodology

Biochemical analysis of hCG in Cork University Hospital was performed using the same hCG immunoassay throughout treatment. The biochemistry laboratory is accredited to ISO15189 (2012) quality standards and participates in external quality assurance. The Abbott Architect™ total β-hCG assay provided a rapid hCG result with the Roche Cobas® Elecsys total and free β-hCG assay providing a confirmatory result. The Roche immunoassay is one of the few hCG assays approved for use in oncology, others are approved for use in early pregnancy only. Post-diagnosis hCG levels were monitored by the specialist GTD nurses and results were communicated to the patients in a timely manner with supportive counselling.

Histopathological assessment of trophoblastic tissue was performed by a perinatal pathologist and diagnosis was made using a combination of clinical history, morphology, and the results of ancillary techniques, where indicated. Ploidy analysis was performed using in-situ hybridisation and molecular genotyping was used to distinguish gestational from non-gestational choriocarcinoma.

Diagnostic imaging of women with GTD was performed in accordance with national clinical guidelines [30] using ultrasound, computed tomography (CT) of the thorax, abdomen and pelvis (CT-TAP) with contrast magnetic resonance imaging (MRI) of the brain where metastatic disease was suspected.

Clinical management was performed according to clinical practice guidelines of the European Organisation for the Treatment of Trophoblastic Diseases (EOTTD) [32]. Following evacuation of the retained produces of conception (ERCP), hCG levels normalised in most women without the need for chemotherapy. When indicated, single agent chemotherapy was prescribed according to national regimens (i.e. methotrexate (MTX) 50 mg intramuscular (IM) on days 1,3, 5, and 7 or Actinomycin-D (ACTD) 2 mg intravenous (IV) bolus every 14 days) [33,34]. Women who progressed to Gestational Trophoblastic Neoplasia (GTN) had FIGO staging and WHO modified prognostic scoring to aid selection of multi-agent chemotherapy. Challenging cases were discussed at MDT and escalated to external review by experts in international GTD networks where warranted.

Results

The characteristics of the five cases reviewed for this study are presented in Table 1. The impact of a national GTD centre in the clinical management of these cases is presented in Table 2. The salient lessons learnt from GTD to aid rare tumour management are presented in Table 4.

Case One: Ectopic Molar Pregnancy

A 40-year-old female presented with irregular periods 18 months postpartum. Despite a tubal ligation she had a positive pregnancy test 4 weeks after unprotected intercourse. On presentation, her serum hCG level was 6889 IU/L which fell to 3740 IU/L, 4 weeks later (Fig. 1).

Table 1
Characteristics of GTD and non-GTD cases.

Case	G, P	Age/years	Disease classification	Subtype	FIGO score	Treatment	Treatment/surveillance period
1	G5P4	40	Molar Pregnancy	Ectopic	NA	MTX, ACTD, EMACO TAHBSO, TP/TE	4 years
2	G0P0	22	Germ Cell Tumour	Ovarian Dysgerminoma	NA	MTX, RPO, RSO	1 year
3	G3P1	32	Choriocarcinoma	Non-gestational	8	CE, DEM, TAH	>4 years
4	G1P1	35	Choriocarcinoma	Gestational	14	MTX, RML, BEP, EMACO	>4 years
5	G3P2	32	Choriocarcinoma	Gestational	16	DEM, CP/PE	>4 years

G = Gravidity; P = Parity. FIGO = The International Federation of Gynaecology and Obstetrics; FIGO score is used to stratify women into low/high risk categories of Gestational Trophoblastic Neoplasia; Low risk ≤ 6, High Risk ≥ 7, Ultra-high risk > 12.
MTX = Methotrexate; ACTD = Actinomycin D; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine; TAHBSO = Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy; RPO = Right Partial Oophorectomy; RSO = Right Salpingo-Oophorectomy; CE = Cisplatin and Etoposide; DEM = Dactinomycin, Etoposide, Methotrexate; TAH = Total Abdominal Hysterectomy TP/TE = Paclitaxel-Cisplatin and Paclitaxel-Etoposide; RML = Right Middle Lobectomy; BEP = Bleomycin, Etoposide and Cisplatin;. CP/PE = Carboplatin and Paclitaxel/Paclitaxel and Etoposide.

Table 2
Impact of a GTD centre on clinical management.

Case	Diagnosis	Impact of GTD service
1	Ectopic Molar Pregnancy	Persistent disease developed after surgical intervention. Lengthy hCG monitoring required. Adherence to GTD clinical practice guidelines.
2	Ovarian Dysgerminoma	Mimic of gestational trophoblastic disease. Alternative diagnosis suspected when unresponsive to methotrexate treatment. Diagnosis of germ cell tumour and surgical excision was curative.
3	Non-gestational Choriocarcinoma	Complexities of refractory disease and role of surgery. Avoidance of unnecessary toxic chemotherapy and long-term sequelae.
4	Gestational Choriocarcinoma	Genotyping required to classify choriocarcinoma. Sub-classification dictated prognosis and treatment pathway. Confirmation of gestational choriocarcinoma informed a switch to multiagent chemotherapy.
5	Gestational Choriocarcinoma	Life-saving therapy, initially induction based, in a new mother with extensive disease. Increased methotrexate dose to achieve central nervous system penetration. Tissue diagnosis not needed and potentially hazardous with risk of haemorrhage. Benefit of international networking.

There was no evidence of pregnancy found at dilation and curettage (D&C) and benign endometrial tissue was identified on histopathological investigation. Two weeks later, serum hCG had risen to 4704 IU/L. Cross sectional imaging demonstrated a 2 cm follicle in the left ovary, consistent with an ectopic molar pregnancy. Following a multidisciplinary meeting (MDM), MTX therapy was initiated according to national clinical guidelines [33]. However, due to fluctuating hCG levels after 9 cycles of MTX, treatment was changed to ACTD as per national guidance [34].

After 2 cycles of ACTD, hCG levels continued to rise and persistent disease in the left ovary was noted on imaging. A multidisciplinary decision was made to switch treatment to etoposide-MTX-ACTD- cyclophosphamide and vincristine (EMACO) [35]. Pre-treatment hCG levels 240 days after initial presentation were 1174 IU/L declining to 10 IU/L after 3 cycles of chemotherapy, but hCG levels rose to 54 IU/L after an additional 2 cycles.

MRI of the pelvis revealed an enhancement in myometrium and a 9 mm right adnexal cyst. Following additional MDM discussion, a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) was performed one year after initial presentation. The hCG level post-operatively was 196 IU/L but rose to 376 IU/L, 665 IU/L, 1488 IU/L and 3208 IU/L at 16, 17, 18 and 19 months respectively, after presentation. Fourth line chemotherapy with paclitaxel-cisplatin and paclitaxel-etoposide (TP/TE) [36] was initiated 19 months after initial presentation and hCG levels normalised 3 months later. Ultimately, chemotherapy was completed 2 years post-presentation, and the patient remains disease free on 2-year follow-up.

Case Two: Ovarian Dysgerminoma

A 22-year-old female with a background history of polycystic ovary syndrome (PCOS) presented with nausea and a positive pregnancy test, despite oral contraceptive use. Serial hCG measurements over four weeks were 6.1 IU/L, 8.5 IU/L, and 13 IU/L. A pelvic ultrasound demonstrated an empty uterus and cystic ovaries. In the subsequent 4 weeks, hCG levels declined to 11.2 IU/L and 7.3 IU/L. The patient was lost to follow up and re-presented 5 months after initial presentation with hCG levels of 284 IU/L (Fig. 2). MTX treatment was commenced [33], but hCG levels rose after a brief decline and concern was raised for a germ cell tumour rather than GTD. Cross-sectional imaging was normal. Following MDM discussion, combined oral contraceptive was initiated for 3 months without a treatment break.

Subsequent MRI of the pelvis revealed a 2.8 cm solid right adnexal mass suspicious of sex cord stromal tumour. Fifteen months after initial presentation, the lady had a right partial oophorectomy performed with subsequent decline in hCG from 263 IU/L to 73 IU/L. Following surgery, hCG rose again to a peak of 131 IU/L and a completion right salpingo-oophorectomy was performed. Histopathological examination revealed an ovarian dysgerminoma and adjuvant therapy was not indicated. Two years post-oophorectomy, hCG levels remain normal (<1 IU/L). The rationale for inclusion of this case in the case series is that ovarian dysgerminoma is a great mimic of GTD, and this case provides valuable lessons in clinical management.

Case Three: Non-gestational Choriocarcinoma

A 32-year-old female with a past medical history of caesarean section presented with irregular vaginal bleeding for several months and a positive pregnancy test. A pelvic ultrasound showed no heartbeat or yolk sac. Eight weeks later, computerised tomography (CT) of the thorax, abdomen, and pelvis (CT-TAP) showed a 3.7 cm mass within the cervix. A follow-up MRI of the pelvis confirmed a heterogenous tumour centred in the posterior aspect of the cervix with elevated hCG at 110,340 IU/L (Fig. 3).

After multidisciplinary discussion, a laparoscopy and cervical mass biopsy confirmed choriocarcinoma involving the cervical mucosa with a FIGO score of 8 (Table 3). Diagnosis was made eight months after initial presentation. The patient was commenced on chemotherapy with etoposide and cisplatin (CE) and hCG dropped to 9657 IU/L after 3 cycles

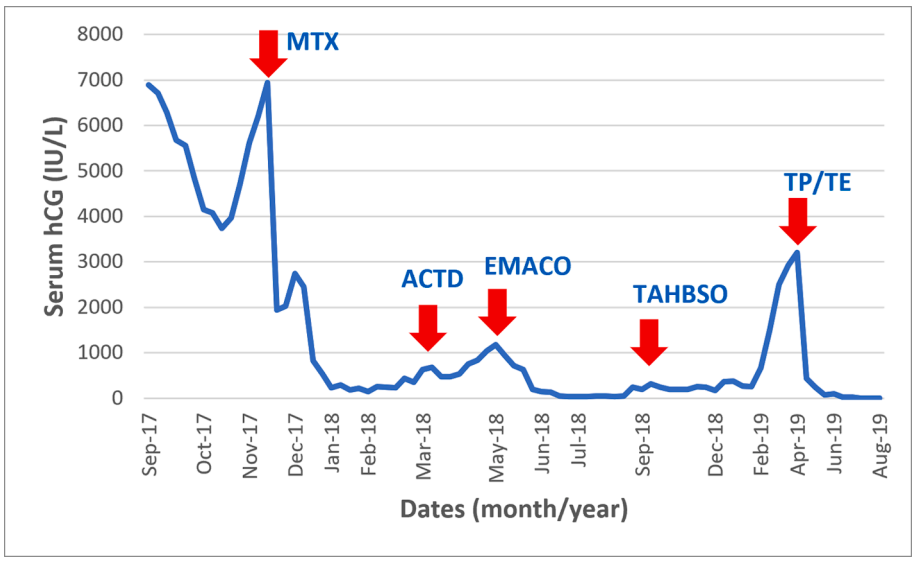


Fig. 1. Graph illustrating the change in hCG levels over time based on chemotherapy and surgical intervention. MTX = Methotrexate; ACTD = Actinomycin-D; EMACO = Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Vincristine; TAHBSO = Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy; TP/TE = Paclitaxel-Cisplatin and Paclitaxel-Etoposide.

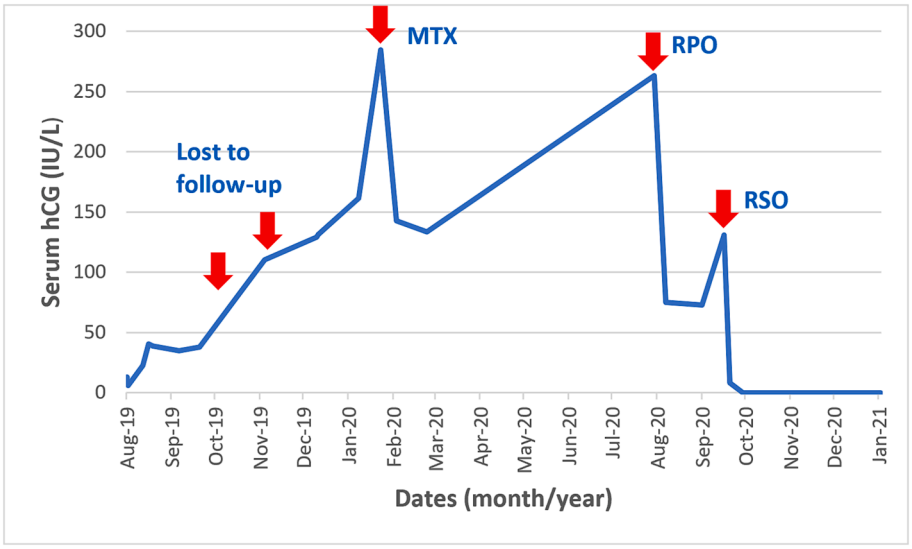


Fig. 2. Graph illustrating the change in hCG levels over time in response to chemotherapy and surgical interventions. MTX = Methotrexate; RPO = Right Partial Oophorectomy; RSO = Right Salpingo-Oophorectomy.

(Fig. 3). Subsequently the patient received EMACO [35] and a further drop in hCG was observed (6 IU/L), 5 weeks after the first cycle of chemotherapy.

A second cycle of EMACO treatment was withheld to mitigate the complications of chemotherapy; neutropenia, infection, and arachnoiditis. At 15-months post-diagnosis, hCG levels were below 1.0 IU/L. Two months later, hCG started to rise again to 1382 IU/L. Repeat ultrasound of the pelvis was suggestive of a vascular cervical mass. Cross-sectional imaging showed no metastatic disease and hysterectomy was advised following MDM discussion. Following a total abdominal hysterectomy, hCG levels dropped to 374 IU/L. One-month post-surgery, there was a further drop in hCG levels to 22 IU/L, with levels ultimately normalising (<1 IU/L) and remaining normal in follow-up surveillance monitoring for 2 years.

Case Four: Gestational Choriocarcinoma

A 35-year-old female with a background history of inflammatory bowel disease presented with a history of abnormal vagina bleeding. [37] Serial hCG measurements raised the possibility of an ectopic pregnancy. An ultrasound of the pelvis showed no visible intra- or extra-uterine pregnancy but the hCG level was elevated at 400 IU/L (Fig. 4). A diagnosis of pregnancy of unknown location (PUL) was made and the lady received 2 doses of IM MTX [33] as per institutional protocol which failed to result in a consistent fall in hCG levels. hCG levels dropped from 496 IU/L to 150 IU/L following the second dose of MTX but then very quickly rose again to 1110 IU/L and reached 1685 IU/L after 7 weeks. Repeat ultrasound examination failed to locate a pregnancy.

Laparoscopy with concurrent dilation and endometrial curettage (D&C) showed no evidence of ectopic pregnancy and there was no significant abnormality detected. Histopathological examination of the D&C tissue demonstrated a proliferative endometrium with no evidence

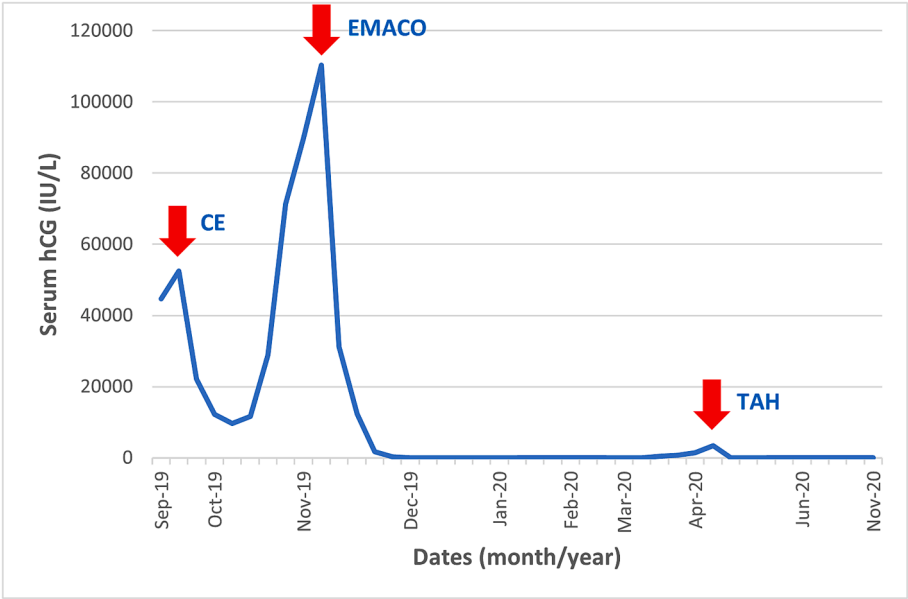


Fig. 3. Graph illustrating the change in hCG levels over time in response to chemotherapy and surgical interventions. CE = Cisplatin and Etoposide; EMACO = Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Vincristine; TAH = Total Abdominal Hysterectomy.

Table 3
FIGO staging and WHO modified prognostic scoring system for Gestational Trophoblastic Neoplasia.

FIGO stage	Description			
I	Gestational trophoblastic tumours strictly confined to the uterine corpus			
II	Gestational trophoblastic tumours extending to the adnexa or to the vagina, but limited to the genital structures			
III	Gestational trophoblastic tumours extending to the lungs with or without genital tract involvement			
IV	All other metastatic sties			
Risk scores	**0**	**1**	**2**	**4**
Age	<40	>40	–	–
Antecedent Pregnancy	Mole	Abortion	Term	
Interval from index pregnancy, months	<4	4–6	7–12	>12
Pre-treatment hCG mIU/ml	$<10^3$	$>10^3$-10^4	$>10^4$-10^5	$>10^5$
Largest tumour size including uterus[a], cm	–	3–4	≥5	–
Site of metastases including uterus	Lung	Spleen, Kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

To stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g., Stage I:4, Stage IV:9. This stage and score will be allotted for each patient. hCG = human chorionic gonadotrophin [a]Size of the tumour in the uterus. Reproduced with permission by FIGO Committee on Gynecologic Oncology [60].

of pregnancy. An MRI of the pelvis confirmed this finding and showed multiple ovarian follicles. A CT of the abdomen and pelvis demonstrated a 1.6 cm enhancing lesion adjacent to the right atrium, and the case was discussed in a thoracic MDM.

A cardiac MRI revealed a lesion that appeared distinct from the pericardium, and a positron emission tomography (PET) scan revealed a low-level ^{18}F-fluorodeoxyglucose (FDG)-avid nodule adjacent to the right heart border with a maximum standardised uptake value (SUV max) of 2.4 reflecting low tumour aggressiveness. Ten weeks post-diagnosis, the lady underwent a lobectomy with partial excision of the right upper lobe, and lymphadenectomy. Histology demonstrated a necrotic lesion extending to the surface of the pleura, and the tumour appeared to occur in the bronchus. The tumour had features of trophoblastic differentiation and was positive for hCG on immunohistochemistry favouring a choriocarcinoma.

A month post-surgery, hCG was still elevated at 2417 IU/L. The patient recovered from her cardiothoracic surgery and adjuvant chemotherapy of Bleomycin, Etoposide and Cisplatin (BEP) was administered in accordance with national guidelines [38] following MDM discussion. Chemotherapy was changed to EMACO [35] on receipt of the genotyping results which confirmed gestational choriocarcinoma as this was felt to be more GTD guideline concordant [30,32,39,40] and hCG levels normalised (<1.0 IU/L) and remains normal during follow-up surveillance. This unusual case highlights the need to closely monitor hCG levels following a PUL to detect disease persistence and diagnose GTN which is the most curable of all gynaecological malignancies.

Table 4
Lessons learnt from gestational trophoblastic disease to aid rare tumour management.

Centre Roles & Resource Benefits	Dedicated Nursing Service	Central Registration
National MDT Lead	Nurse liaison	Mandatory registration
Network establishment	Facilitates monitoring of care pathway	Quantify clinical cases nationally
Guideline Development	Psychological support for patients	Facilitate audit
Patient Participation & Involvement		Equity of access to care and advice
Clinical trial availability		
Clinical resource for management guidance		

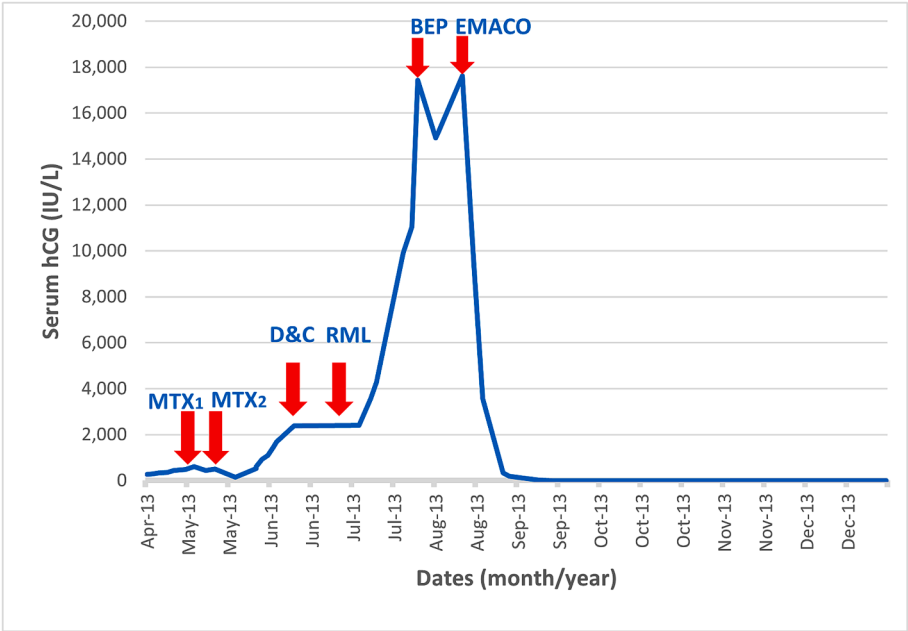


Fig. 4. Graph illustrating the change in hCG levels over time in response to chemotherapy and surgical interventions. MTX = Methotrexate; D&C = Dilation and Curettage; RML = Right Middle Lobectomy; BEP = Bleomycin, Etoposide and Cisplatin; EMACO = Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Vincristine.

Case Five: Gestational Choriocarcinoma

A 32-year-old female presented to her general practitioner (GP) 7-weeks postpartum. Following delivery of healthy twin boys at 35 weeks' gestation, she complained of right sided abdominal pain and redness in her left eye. Routine bloods were performed and revealed abnormal liver function tests (LFTs) and a haemoglobin of 8.0 g/dL, which were normal post-delivery. She was referred to the local hospital for medical assessment. On arrival, she had further investigations including a chest x-ray which revealed multiple bilateral pulmonary metastases and a hCG level of 507,150 IU/L. Her CT scan demonstrated diffuse necrotic pulmonary, liver, splenic, and nodal metastatic disease. MRI brain imaging demonstrated multiple intraparenchymal brain metastases. MRI pelvis confirmed the presence of 2 large necrotic masses

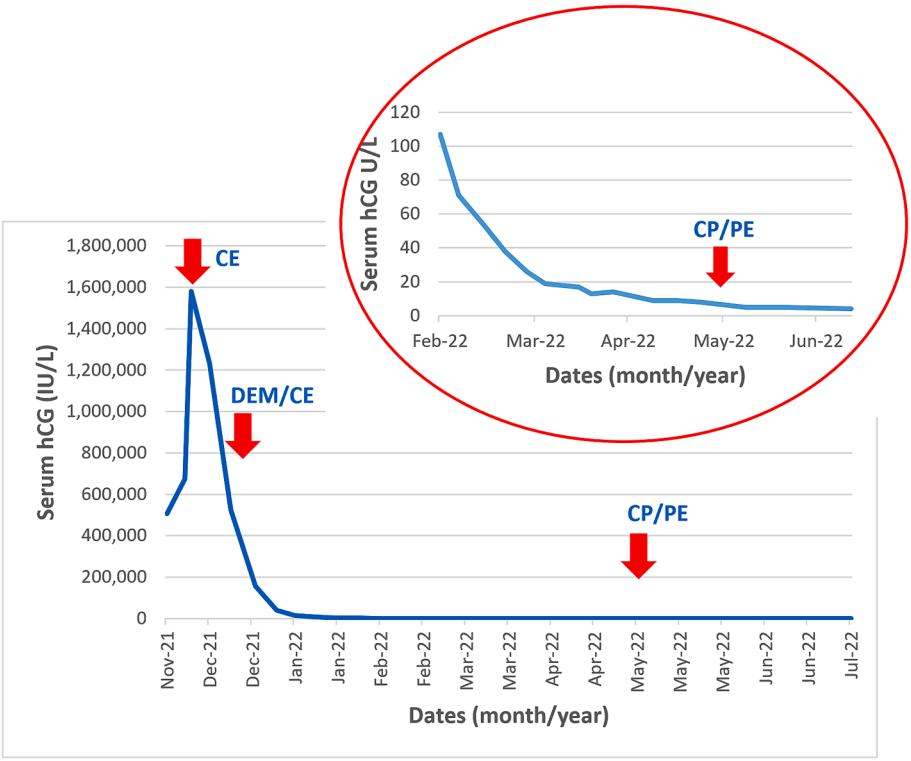


Fig. 5. Graph illustrating the change in hCG levels over time in response to chemotherapy. CE = Cisplatin Etoposide; DEM = Dactinomycin, Etoposide, Methotrexate. CP/PE = Carboplatin and Paclitaxel/Paclitaxel and Etoposide. Inset figure shows plateauing of hCG levels in May 2022.

within the myometrium, measuring 6.0 × 5.7 cm and 5.4 × 5.5 cm.

An initial liver biopsy was non-diagnostic and placental histology from her recent pregnancy was unremarkable, showing no evidence of intra-placental choriocarcinoma. These findings culminated in a diagnosis of an ultra-high risk choriocarcinoma with a FIGO score of 16 (Table 3). The patient was transferred to a specialist tertiary centre to begin intensive chemotherapy (Fig. 5). She received 3 cycles of induction chemotherapy, with a 2-day regimen of etoposide (100 mg/m2 IV D1-2) and cisplatin (20 mg/m2 IV D1-2).[41] She then proceeded to treatment with combination chemotherapy comprised of dactinomycin (0.5 mg IV bolus D1), etoposide (100 mg/m2 IV D1), methotrexate (300 mg/m2 IV D1) (DEM), and folinic acid (15 mg PO D2,3) alternating with etoposide (150 mg/m2 IV D8) and cisplatin (75 mg/m2 IV D8).[42].

After several cycles of chemotherapy, she developed cisplatin-induced ototoxicity with tinnitus and moderate-to-severe hearing loss in both ears. Six-months after her original presentation, her hCG plateaued at 9 IU/L and her case was discussed at the EOTTD Annual Meeting and treatment was changed to carboplatin (AUC4 IV D1) (rather than Cisplatin to abrogate further ototoxicity) and paclitaxel (135 mg/m2 IV D1) alternating with paclitaxel (135 mg/m2 IV D15) and etoposide (150 mg/m2 IV D15). Her hCG normalized for the first time approximately 3 weeks after this change in chemotherapy and she remains in remission during follow-up surveillance.

Discussion

The cases selected for this review reflect the complexity of managing women with GTD. It highlights the important role of an expert GTD centre and integrated MDT approach, further enhanced by experts from other GTD centres to manage women with this rare disorder and improve patient outcomes.[27,43,44] These range from challenges in differentiating the condition from other causes of hCG elevation to the treatment of critically ill patients where initial chemotherapy treatment can lead to fatal haemorrhage. The gravity of managing such cases is also reflected in the fact that many will have dependants or be hoping to initiate a family. The “Goldilocks Zone” (i.e. not too much treatment which will compromise quality of survival and not too little treatment which will compromise cure) for such cases is narrow [45], and the transgenerational impact of successful management is substantial. The challenge is to achieve an early cure in these women with the least toxicity. [46].

Cancer is a lonely illness. During the consultative phase of the National Cancer Strategy 2017–2026 patients with rare cancers consistently commented on how this isolation was compounded by the lack of information on their cancer type. In the present study, patients had regular access to nurse specialists who recorded the progress of their illness, and to a multidisciplinary team with a global outreach to guide therapy.[47,48] This was particularly relevant to case five where international discussion guided management and reassured the patient about her treatment plan, and to case one whose treatment duration was 2 years.

As with other more common cancers, Irish, European and United States based consensus guidelines are established for patients with GTD. [30,39,40,49] These have evolved from the EOTTD Clinical Working Party, founded in Lyon, France in 2010.[32,50] This occurred 7 years before the European Rare Cancer Network was established.[51] As an exemplar in the area of rare tumour management, the EOTTD have standardised management plans through consensus, clinical trials and real-world data. Reviews of practices in specific countries, such as the UK [39], Belgium [52], Switzerland [53], and Ireland [29], have been published in recent years. These reviews generally concur, as intoned above, that national registration and treatment programmes and databases are quite effective in ensuring that there is effective information sharing among clinicians that are treating GTD despite the rareness of the disease complex.

In Ireland, a similar strategy for other rare tumours would include the assignment of a national clinical lead integrated with consensus working groups, with dedicated nurse specialist support conducted virtually who could also serve as nurse navigators to guide management and orchestrate care. Such a strategy would acknowledge the challenges patients face in dealing with multidisciplinary cancer management which requires a degree of self-reliance, and where adverse events can occur when self- reliance is missing.[54,55] Navigating care without a compass can also increase psychological distress, worsening cancer outcomes.[56] A specialist centre would also help address the concerns highlighted by 25% of GTD patients in our centre who reported deficits in the understanding of their condition by medical professionals with whom they interacted outside the centre.[29].

In the context of extrapolating our current findings to the development of treatment strategies for other rare cancers, it is important to realize that GTD has a measurable biomarker (hCG) that is strongly correlated to tumour burden and causally related to the ultimate survival of patients. However, this is not true for several types of rare tumours such as cholangiocarcinoma [57,58] and may be the rule rather than the exception in rare cancers, for which the use of networking and cancer registries has been strongly suggested as approaches to improve patient survival.[59].

Conclusion

The cases presented here highlight the critical learning that is emerging for the treatment of rare cancers. The treatment pathways and clinical outcome of these cases demonstrate the importance of a national GTD centre with an expert clinical lead, dedicated nurse support and multi-disciplinary group adhering to national clinical guidelines to improve the outcome for women with this rare disorder. Importantly, within the ethos of the GTD centre patient participation and involvement is embedded. Moreover, the GTD centre fully integrates and networks with international colleagues, databases, and organisations for the management of rare cancers (e.g., EURACAN). Critical to the establishment of this national programme for rare disease is the need for registration to be mandatory, to allow equity of access for all patients to guideline-based care in an expert centre to ensure optimum patient management.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Caroline M Joyce reports financial support was provided by Irish Research Council.

Acknowledgements

The authors wish to express their gratitude to the patients and their families who made this publication possible. Special thanks also to the scientific, nursing, and medical staff in Cork University Hospital and Cork University Maternity Hospital for their contribution to this work.

Funding

CMJ is funded by the Irish Research Council under grant number EBPPG/2021/38. The sponsor was not involved in the study design or manuscript preparation.

Guarantor

SOR.

Author contributions

Study design: SOR, MH, CMJ and HKC; Study data collection: MH,

CMJ and CK.

Graphs: CMJ; Drafting manuscript; SOR, MH and CMJ.

Approval of final version of manuscript: SOR, MH, CJ, HKC, CK, SM, MKON and JC.

Ethics approval

Written informed consent was obtained from all patients participating in this study.

References

[1] Gatta G, Capocaccia R, Botta L, Mallone S, De Angelis R, Ardanaz E, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study. Lancet Oncol 2017;18(8):1022–39.

[2] Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, et al. Rare cancers are not so rare: The rare cancer burden in Europe. Eur J Cancer 2011;47(17):2493–511.

[3] National Center for Advancing Translational Science. Rare Disease List [Internet]. Available from: https://rarediseases.info.nih.gov/RareDiseaseList.aspx.

[4] Department of Health and Children. National Cancer Strategy 2017-026 [Internet]. Available from: https://assets.gov.ie/9315/6f1592a09583421baa87de3a7e9cb619.pdf.

[5] Pillai RK, Jayasree K. Rare cancers: challenges & issues. Indian J Med Res 2017;145(1):17.

[6] Majd N, Penas-Prado M. Updates on management of adult medulloblastoma. Curr Treat Options Oncol 2019;20:1–24.

[7] Sin-Chan P, Li BK, Ho B, Fonseca A, Huang A. Molecular classification and management of rare pediatric embryonal brain tumors. Curr Oncol Rep 2018;20:1–11.

[8] Shrivastava SBL, Agrawal G, Mittal M, Mishra P. Management of vaginal cancer. Rev Recent Clin Trials 2015;10(4):289–97.

[9] Tan S-B, Dear KBG, Bruzzi P, Machin D. Strategy for randomised clinical trials in rare cancers. BMJ 2003;327(7405):47–9.

[10] Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, Stiller CA, Coebergh JWW. Cancer in children and adolescents in Europe: developments over 20 years and future challenges. Eur J Cancer 2006;42(13):2183–90.

[11] de Heus E, Duijts SFA, van der Zwan JM, Kapiteijn E, Nieveen van Dijkum EJM, van Herpen CML, et al. The gap between rare and common cancers still exists: Results from a population-based study in the Netherlands. Eur J Cancer [Internet] 2022;167:103–11.

[12] Tumiene B, Kristoffersson U, Hedley V, Kääriäinen H. Rare diseases: past achievements and future prospects. J Community Genet 2021;12(2):205–6.

[13] Ray-Coquard I, Pujade Lauraine E, Le Cesne A, Pautier P, Vacher Lavenue MC, Trama A, et al. Improving treatment results with reference centres for rare cancers: Where do we stand? Eur J Cancer [Internet] 2017;77:90–8.

[14] Bogaerts J, Sydes MR, Keat N, McConnell A, Benson Al, Ho A, et al. Clinical trial designs for rare diseases: Studies developed and discussed by the International Rare Cancers Initiative. Eur J Cancer 2015;51(3):271–81.

[15] Keat N, Law K, Seymour M, Welch J, Trimble T, Lascombe D, et al. International Rare Cancers Initiative. Lancet Oncol [Internet] 2013;14(2):109–10. https://doi.org/10.1016/S1470-2045(12)70570-3. Available from:.

[16] Strickland AL, Gwin K. Gestational trophoblastic disease- rare, sometimes dramatic, and what we know so far. Available from Semin Diagn Pathol [Internet] 2022;39(3):228–37. https://www.sciencedirect.com/science/article/pii/S0740257022000223.

[17] Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet [Internet] 2010;376(9742):717–29. https://doi.org/10.1016/S0140-6736(10)60280-2. Available from:.

[18] Fisher RA, Maher GJ. Genetics of gestational trophoblastic disease 2021;Vol. 74:29–41.

[19] Ronnett BM. Hydatidiform moles: differential diagnosis, diagnostic reproducibility, genetics and ancillary techniques to refine diagnosis. Diagnostic Histopathol [Internet] 2019;25(2):35–52. https://doi.org/10.1016/j.mpdhp.2018.12.003.

[20] Kaur B. Pathology of gestational trophoblastic disease (GTD). Best Pract Res Clin Obstet Gynaecol [Internet] 2021;74:3–28.

[21] Usui H. Auxiliary and experimental diagnostic techniques for hydatidiform moles. J Obstet Gynaecol Res 2022;48(12):3077–86.

[22] Buza N. Gestational Trophoblastic Disease: Contemporary Diagnostic Approach. Surg Pathol Clin [Internet]. 2022; Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2018264560&from=export.

[23] Berkowitz, R.S., Horowitz D.P., Elias KM. Hydatidiform mole: Epidemiology, clinical manifestations and diagnosis. UpToDate, Post TW(Ed) UpToDate, Waltham, MA (Accessed June 19, 2022). 2022.

[24] WHO Classification of Tumours Editorial board ed. World Health Organisation Classificaiton of Tumours. 5th ed. Female Genital Tumours. Lyon: IARC Press; 2020.

[25] Eysbouts YK, Bulten J, Ottevanger PB, Thomas CMG, ten Kate-Booij MJ, van Herwaarden AE, et al. Trends in incidence for gestational trophoblastic disease over the last 20 years in a population-based study. Gynecol Oncol [Internet] 2016;140(1):70–5.

[26] Schmid P, Nagai Y, Agarwal R, Hancock B, Savage PM, Sebire NJ, et al. Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study. Available from Lancet [Internet] 2009;374(9683):48–55. https://www.sciencedirect.com/science/article/pii/S0140673609606188.

[27] Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynecol Obstet 2021;155(S1):86–93.

[28] Freitas F, Braga A, Viggiano M, Velarde LGC, Maesta I, Uberti E, et al. Gestational trophoblastic neoplasia lethality among Brazilian women : A retrospective national cohort study. Gynecol Oncol [Internet] 2020;158(2):452–9. https://doi.org/10.1016/j.ygyno.2020.04.704. Available from:.

[29] Joyce CM, Coulter J, Kenneally C, Mccarthy TV, Donoghue KO. Experience of women on the Irish National Gestational Trophoblastic Disease Registry. Eur J Obstet Gynecol Reprod Biol [Internet] 2022;December 2021(272):206–12. https://doi.org/10.1016/j.ejogrb.2022.03.039.

[30] National Cancer Control Programme. Diagnosis, staging and treatment of patients with gestational trophoblastic disease: National Clinical Guideline No. 13. Dep Heal Irel (An Roinn Slainte) [Internet]. 2022;May(13). Available from: https://health.gov.ie/wp-content/uploads/2015/12/GTD-Guideline-Full_FINAL-APPROVED-FOR-WEB.pdf.

[31] Singh K, Rollins S, Ireson J. Gestational trophoblastic disease: best practice nursing guidelines. Available from: Gynecol Obstet Invest [Internet] 2023. https://www.karger.com/DOI/10.1159/000530570.

[32] Lok C, van Trommel N, Massuger L, Golfier F, Seckl M, Abreu MH, et al. Practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease. Eur J Cancer 2020;130:228–40.

[33] National Cancer Control Programme. Methotrexate 8 day Charing Cross Regimen [Internet]. [cited 2023 Mar 4]. Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/gynaecology/246-methotrexate-8-day-charing-cross-regimen.pdf.

[34] National Cancer Control Programme. DACTINomycin Therapy [Internet]. [cited 2023 Mar 4]. Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/gynaecology/247-dactinomycin-therapy.pdf.

[35] National Cancer Control Programme. Etoposide, Methotrexate, DACTINomycin, Cyclophosphamide, vinCRIStine (EMA/CO) Therapy [Internet]. [cited 2023 Mar 4]. Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/gynaecology/248-ema-co-therapy-etoposide-methotrexate-dactinomycin-cyclophosphamide-vincristine-.pdf.

[36] National Cancer Control Programme. Paclitaxel-cisplatin alternating with paclitaxel-etoposide (TP/TE) [Internet]. [cited 2023 Mar 4]. Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/gynaecology/266-paclitaxel-cisplatin-alternating-with-paclitaxel-etoposide-tp-te-therapy.pdf.

[37] McCarthy CM, Unterscheider J, Burke C, Coulter J. Metastatic gestational choriocarcinoma: a masquerader in obstetrics. Ir J Med Sci 2018;187(1):127–9.

[38] National Cancer Control Programme. Bleomycin, Etoposide and CISplatin (BEP) Therapy [Internet]. [cited 2023 Mar 4]. Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/genitourinary/300-bleomycin-etoposide-and-cisplatin-bep-therapy.pdf.

[39] Tidy J, Seckl M HB. Management of Gestational Trophoblastic Disease: Green-top Guideline No. 38 – June 2020. BJOG. 2021 Feb 1;128:e1–27.

[40] Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C. Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi39–50.

[41] National Cancer Control Programme. CISplatin (75mg/m2) + Etoposide Therapy-21 day [Internet]. [cited 2023 Mar 4]. Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/lung/cisplatin-etoposide.pdf.

[42] National Cancer Control Programme. Etoposide Methotrexate DACTINomycin/Etoposide CISplatin (EMA/EP) Therapy [Internet]. Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/gynaecology/264-ep-ema-therapy-etoposide-cisplatin-etoposide-methotrexate-dactinomycin-.pdf.

[43] Kohorn E. Worldwide survey of the results of treating gestational trophoblastic disease. J Reprod Med 2014;59:145–53.

[44] Coulter J, van Trommel N, Lok C. Ten steps to establish a national centre for gestational trophoblastic disease. Curr Opin Oncol 2021;33(5):435–41.

[45] Broderick A, Carroll HK, O'Riordan K, Jackson A, Macfarlane J, O'Reilly S. Breeching, "The Goldilocks Zone": Tetraplegia as a Rare Life-Altering Infective Complication of Adjuvant Breast Cancer Chemotherapy: Breeching "The Goldilocks Zone". Arch Breast Cancer 2023;10(1):93–8.

[46] Clark JJ, Slater S, Seckl MJ. Treatment of gestational trophoblastic disease in the 2020s. Current Opinion in Obstetrics and Gynecology Lippincott Williams and Wilkins; 2021 p. 7–12.

[47] Joyce CM, Fitzgerald B, McCarthy TV, Coulter J, O'Donoghue K. Advances in the diagnosis and early management of gestational trophoblastic disease. BMJ Med 2022;1(1):e000321.

[48] Frijstein MM, Lok CAR, Coulter J, van Trommel NE, ten Kate – Booij MJ, Golfier F, et al. Is there uniformity in definitions and treatment of gestational trophoblastic disease in Europe? Int J Gynecol Cancer 2019;29(1):108–12.

[49] Abu-Rustum NR, Yashar CM, Bean S, Bradley K, Campos SM, Sook Chon H, et al. Gestational trophoblastic neoplasia, version 2.2019. JNCCN J Natl Compr Cancer Netw 2019;17(11):1374–91.

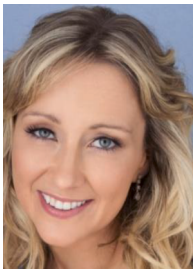
[50] Bolze P-A, Attia J, Massardier J, Seckl MJ, Massuger L, van Trommel N, et al. Formalised consensus of the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases. Eur J Cancer 2015;51(13):1725–31.

[51] European Reference Networks. EURACAN [Internet]. [cited 2023 May 5]. Available from: https://euracan.eu/who-we-are/about-euracan/.
[52] Schoenen S, Delbecque K, Van Rompuy A-S, Marbaix E, Noel J-C, Delvenne P, et al. Importance of pathological review of gestational trophoblastic diseases: Results of the Belgian Gestational Trophoblastic Diseases Registry. Int J Gynecol Cancer 2022;32(6):740–5.
[53] Fehlmann A, Benkortbi K, Rosseel G, Meyer-Hamme U, Tille J-C, Sloan-Béna F, et al. Gestational trophoblastic disease in Switzerland: retrospective study of the impact of a regional reference centre. Swiss Med Wkly 2021;151(0506):w20406.
[54] Bledsaw K, Prudowsky ZD, Yang E, Harriehausen CX, Robins J, DeJean J, et al. A novel oncodental collaborative team: integrating expertise for central line-associated bloodstream infection prevention in pediatric oncology patients. JCO Oncol Pract 2023;19(1):e25–32.
[55] Trosman JR, Carlos RC, Simon MA, Madden DL, Gradishar WJ, Benson AB, et al. Care for a patient with cancer as a project: Management of complex task interdependence in cancer care delivery. J Oncol Pract 2016;12(11):1101–13.
[56] Wu Y, Zhou L, Zhang X, Yang X, Niedermann G, Xue J. Psychological distress and eustress in cancer and cancer treatment: Advances and perspectives. Sci Adv 2022;8(47).
[57] Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen H-J, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol 2022;76(5):1109–21.
[58] Satake T, Morizane C, Rikitake R, Higashi T, Okusaka T, Kawai A. The epidemiology of rare types of hepatobiliary and pancreatic cancer from national cancer registry. J Gastroenterol 2022;57(11):890–901.
[59] Gatta G, Trama A, Capocaccia R, Hackl M, Eycken EV, Henau K, et al. Epidemiology of rare cancers and inequalities in oncologic outcomes. Eur J Surg Oncol 2019;45(1):3–11.
[60] FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. Int J Gynaecol Obstet 2009;105(1):3–4.

Munzir Hamid is a Medical Oncology Specialist Trainee at Cork University Hospital. He is an Adjunct Clinical Lecturer at University College Cork. He is also an Honorary Lecturer at the Faculty of Medicine and Health Sciences of the Royal College of Surgeons of Ireland. Munzir is a graduate of the University of Science and Technology, Sudan (MBBS) and the Royal College of Physicians of Edinburgh (MRCP UK Diploma). He holds certification in Medical Oncology by the European Society for Medical Oncology.

Caroline Joyce is a Principal Clinical Biochemist in Cork University Hospital. She holds an MSc in Biomedical Science from the University of Ulster (1991) and a Diploma in Molecular Genetics from the Royal College of Pathologists, London (2003). She is registered by the European Board of Medical Genetics as a European Clinical Laboratory Geneticist (2017). Caroline is a member of the National Cancer Control Programme Steering Committee for Gestational trophoblastic Disease. She is currently a PhD scholar at University College Cork and is funded by the Irish Research Council to conduct research in Gestational Trophoblastic Disease.

Hailey Carroll is a Medical Oncology Specialist Registrar at Cork University Hospital. She obtained her BSc in Medicine, Health, and Society and Child Development from Vanderbilt University in 2010. She received her medical degree from the Royal College of Surgeons in Ireland (RCSI) in 2016 (MB BCh BAO) and completed her PGDip in Health Profession Education at RCSI in 2017. She is a member of the Royal College of Physicians in Ireland. She has a special interest in gynaecological malignancies including GTD, sarcoma, and adolescent and young adult cancer care.



Caitriona Kenneally is a clinical nurse specialist at the Gestational Trophoblastic Disease Department since its establishment in 2015 in Cork University Maternity Hospital. She graduated from the National University of Ireland, Galway with a BSc in Nursing (1999). She holds a Higher Postgraduate Diploma in Oncology (2020) from University College Cork and a Postgraduate Diploma in Psychology (2011) from Griffith College Cork. She is a member of the International Society for the Study of Trophoblastic Diseases (ISSTD), the European Organisation for Treatment of Trophoblastic Diseases (EOTTD) and the Nurses International Society for the Study of Trophoblastic Diseases (NISSTD).

Stacey Mulcahy is a clinical nurse specialist in the Gestational Trophoblastic Disease Centre based in Cork University Maternity Hospital. She graduated as a Registered General Nurse from University Hospital Bradford in 1986. She holds a postgraduate diploma in Ophthalmology Nursing (Moorfields 1988) and completed a postgraduate in Midwifery in 1991. Stacey has worked as a midwife in Cork University Maternity Hospital since 2008 and as CNS in the GTD Centre, CUMH since 2021. She is a member of the European Organisation for Treatment of Trophoblastic Diseases (EOTTD), the International Society for the Study of Trophoblastic Diseases (ISSTD), and the Nurses International Society for the Study of Trophoblastic Diseases (NISSTD).

Mary-Kate O'Neill is a clinical nurse specialist in the Gestational Trophoblastic Disease Centre based in Cork University Maternity Hospital. She is a UCC nursing graduate (BSc, 2008). Mary-Kate holds a Post Graduate Diploma in Oncology Nursing (UCD, 2012). Mary-Kate has worked as an oncology nurse in Cork University Hospital since 2008 and as CNS in the GTD Centre, CUMH since 2021. She is a member of the European Organisation for Treatment of Trophoblastic Diseases (EOTTD), the International Society for the Study of Trophoblastic Diseases (ISSTD), and the Nurses International Society for the Study of Trophoblastic Diseases (NISSTD).

John Coulter is a practicing Gynaecological Oncologist at the Cork University Maternity Hospital Cork. He is a UCC medical graduate (1989) and attained Fellowship of the Royal College of Surgeons in Ireland (FRCSI) in 1992. After general training in Obstetrics and Gynaecology in Ireland, he travelled to Australia and completed a Fellowship training scheme in Gynaecological Oncology. He is currently a consultant in Cork and is a member of the Cork Gynaecological Oncology Group Multidisciplinary Team. He is a Clinical Lead for Gestational Trophoblastic Disease and a member of the National Cancer Control Program guideline committee on hereditary gynaecological cancers.

Seamus O'Reilly is Consultant Medical Oncologist at Cork University Hospital and Associate Professor of Medicine at University College Cork. He is a graduate of University of Galway (BSc, MB, MD) and Johns Hopkins University (PhD). He is vice clinical lead of Cancer Trials Ireland and Chairperson Cork ARC Cancer Support House and a member of the Executive Board of the Breast International Group.