GESTATIONAL TROPHOBLASTIC DISEASE

K. Sieunarine, J.R. Smith, A. Aylwin and A. Mitchell

Introduction

Gestational trophoblastic disease (GTD) includes a spectrum of cellular proliferation of trophoblasts ranging from the various forms of hydatidiform mole (complete and partial) through invasive moles and the malignant trophoblastic tumours choriocarcinomas to placental site trophoblastic tumours (PSTTs). Gestational trophoblastic tumour (GTT) is the term used for denoting those conditions that require more active intervention, usually chemotherapy and includes invasive moles, choriocarcinomas and placental site tumours.

Staging

An accurate staging and classification system for GTD will enable clinicians to assess the prognosis or risk of patients and to individualize and optimize their treatment. To date there has been a variety of staging and classification systems used by different treatment centres, which has made meaningful comparison of treatment results and the evaluation of new treatment protocols difficult.

Staging should be based on history, clinical examination and appropriate laboratory and radiological studies. Since urinary human chorionic gonadotrophin (hCG) and serum bhCG titres accurately reflect clinical disease, histological verification is not required for diagnosis, although it may aid in therapy.

The classic anatomical staging system for GTD1 of the International Federation of Gynecology and Obstetrics (Federation Internationale Gynecologique Obstetrique or FIGO) describes stage I as disease confined to the uterus and stage II as disease that extends outside of the uterus, but is limited to the genital structures (adnexa, vagina and broad ligament). Stage III refers to disease that extends to the lungs with or without genital tract involvement and stage _V to disease at other metastatic sites (e.g. the liver and brain).

The FIGO Oncology Committee accepted a new revised classification of GTD in March 2002.2 This combined the classic FIGO anatomical staging system with a revised World Health Organization risk factor scoring system3 (see Table 1).

In order to stage and allot a risk factor score, a patient’s diagnosis is allocated to a stage as represented by a Roman numeral I to IV (Table 7.1). This is then separated from the sum of all the actual risk factor scores by a colon (Table 7.2), e.g. stage FIGO IV: 13. For the purposes of reporting patients are divided into high-risk (score of ≥7) and low-risk (score of 0–6) groups.

PSTTs and their non-malignant counterparts are excluded.

Principal Investigations

Histopathology

This will normally be available for patients who have had a molar pregnancy and in most cases of non-molar pregnancies.

Human chorionic gonadotrophin estimations

This provides the key to monitoring the activity of the disease, its response to treatment and follow-up.

Ultrasound

Ultrasound with Doppler assessment should be routine in managing these patients. In the pelvis the uterine size and volume can be measured, which may provide an important potential prognostic variable.4 Doppler ultrasound can assess the vascularity of the disease. A low pulsatility index in the uterine arteries (as measured by Doppler ultrasound) correlates with the development of drug resistance in the tumour.4 One study confirmed that, if the pulsatility index in the uterine arteries is <1, this significantly correlates with the development of resistance to methotrexate chemotherapy in low-risk patients.5 The liver should also be scanned for
hepatic metastases. Theca lutein cyst size and persistence correlate with the development of post-molar GTD.

Chest X-ray
Chest X-ray is appropriate for diagnosing lung metastases (for example, from invasive moles or choriocarcinomas). Low-risk patients are usually managed on the basis of a chest X-ray. It is the chest X-ray that is used for counting the number of lung metastases to evaluate the risk factor score not the computed tomography (CT) scan (see page 29).

Computed tomographic scanning
Although CT scanning of the chest is more sensitive than a chest X-ray, the whole body is not routinely CT scanned unless there are clinical indications, e.g. headache. In high-risk patients the delineation of metastatic disease sites (intra-abdominal, lung, liver and brain) by CT scanning is important in determining management.

Magnetic resonance imaging scanning
Magnetic resonance imaging (MRI) is the investigation of choice if central nervous system (CNS) metastases are suspected. MRI should be performed if cerebral metastases are suspected, even when the CT scan is normal. MRI detects lesions missed on a CT scan, particularly in the posterior fossa. MRI can play a role in management for determining tumour involvement of the great vessels and urinary and gastrointestinal tracts, before possible surgery.

Lumbar puncture
Patients with pulmonary disease are at risk of developing brain metastases and some oncologists find hCG estimations of the cerebrospinal fluid very useful in detecting metastatic disease when the scans are normal.6

One of the main reasons for current treatment success is the inherent chemosensitivity of GTD and GTTs.

Given its efficacy and safety profile, methotrexate/folinic acid remains the treatment of choice for low-risk patients (see Table 2).

For relapsed patients (high risk) or with disease resistant to EMA/CO (actinomycin D, etoposide and methotrexate/vincristine (oncovin) and cyclophosphamide), the EP/EMA regime is used, which is etoposide and cisplatin alternating weekly with methotrexate, actinomycin D and etoposide (see Table 2). The development of drug resistance is one of the main causes of treatment failure.

Surgery can be an important component of salvage treatment and often may be clearly therapeutic. Surgery plays an important role in the primary treatment of patients with PSTTs since PSTTs have rather variable chemosensitivity. Hysterectomy is the treatment of choice for PSTTs limited to the uterus.

The role of radiotherapy is uncertain; however, there is a role for stereotaxic radiotherapy in the occasional case where there is a single site of relapse.

After completion of chemotherapy patients are monitored by serial hCG estimations. CT and MRI scanning allow better localization of sites of resistant disease. MRI is suitable for disease within the pelvis and brain whilst CT scanning is appropriate for the chest and abdomen.
References


Further reading


GESTATIONAL TROPHOBLASTIC DISEASE

† The FIGO staging system + FIGO risk factor scoring system

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>FIGO risk factor scoring values</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;40</td>
<td>≥ 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Molar</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval from index pregnancy (months)</td>
<td>&lt;4</td>
<td>4 ≤ 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment serum HCG (IU/l)</td>
<td>&lt;10³</td>
<td>10³ – &lt;10⁴</td>
<td>10⁴ – &lt;10⁵</td>
<td>≥ 10⁵</td>
<td></td>
</tr>
<tr>
<td>Largest tumour size (including uterus) (cm³)</td>
<td>&lt;3</td>
<td>3 ≤ 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen and kidney</td>
<td>Gastrointestinal</td>
<td>Liver and brain</td>
<td></td>
</tr>
<tr>
<td>Number of metastases</td>
<td>–</td>
<td>1 – 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† American Joint Committee on Cancer surgical staging system

<table>
<thead>
<tr>
<th>AJCC T Stage</th>
<th>T1</th>
<th>T1</th>
<th>T1</th>
<th>T2</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>No risk factors</td>
<td>One risk factor</td>
<td>Two risk factors</td>
<td>No risk factors</td>
<td>One risk factor</td>
</tr>
</tbody>
</table>

TNM definitions

Primary tumour (T).
T1: disease limited to the uterus.
T2: disease outside of the uterus but is limited to genital structures (the ovary, tube, vagina and broad ligaments).

Regional Lymph Nodes (N).
There is no regional nodal designation (N classification) in the staging of gestational trophoblastic tumors. Nodal involvement in these tumors is rare but has an extremely poor prognosis. Nodal metastases should be classified as metastatic M1b disease.

Distant metastasis (M).
M1a: Lung metastasis
M1b: All other distant metastasis

Risk factors affecting staging include the following:
1. hCG > 100,000 IU/24-hour urine.
2. The detection of disease more than 6 months from termination of the antecedent pregnancy.

Longitudinal ultrasound sections of the pelvis showing a large heterogeneous echogenic tumour confined to the uterus (stage I). (a) Grey scale image and (b) power Doppler image demonstrating marked vascularity of the tumour.

Longitudinal ultrasound sections of the pelvis. (a) Non-visible tumour and (b) power Doppler image showing the increased vascularity of a small stage I trophoblastic lesion (arrow).

Transverse ultrasound image with colour Doppler of the uterus in a patient with a stage I tumour, with pulse wave Doppler of the left uterine artery demonstrating a low (<1.0) pulsatility index (PI = peak systolic – diastolic velocity/mean) due to the reduced end organ resistance characteristic of gestational trophoblastic tumours.

Digital subtraction angiogram of the pelvis with a catheter in the right uterine artery showing the significant vascularity of a stage I tumour (arrow), secondary to neoangiogenesis.

Longitudinal ultrasound sections of the pelvis showing a large heterogeneous left-sided uterine mass (yellow arrow) extending along the broad ligament to the left ovary (white arrow) (stage II).

Sagittal T2-weighted image of the pelvis in a patient with a large heterogeneous stage I uterine tumour (yellow arrow). Note fluid within the obstructed endometrial cavity (white arrow).
GESTATIONAL TROPHOBLASTIC DISEASE

III + the sum of FIGO risk factor scoring values
Disease extends to the lungs with or without known genital tract involvement

T2 Two risk factors

T3 M1a No risk factors

T3 M1a One risk factor

T3 M1a Two risk factors

IV + the sum of FIGO risk factor scoring values
Disease at other metastatic sites

any T M1b No risk factors

any T M1b One risk factor

any T M1b Two risk factors

(a) Chest radiograph demonstrating multiple pulmonary metastases (stage III).
(b) Axial CT scan of the chest (lung windows) of the same patient.

Axial CT scan of the pelvis showing a heterogeneous mass (arrowhead) arising from the uterus and invading the bladder (arrow) (stage IV tumour).

Intravenous contrast-enhanced CT of the liver demonstrating multiple hypodense and splenic metastases (stage IV).

Gadolinium-enhanced axial T1-weighted MRI of the brain showing two metastases, one cystic and rim enhancing (arrow) and the other solid and heterogeneously enhancing (arrowhead) (stage IV).