Histopathological classification of Gestational Trophoblastic Disease

- Hydatidiform mole - complete
- partial

- Invasive hydatidiform mole

- Choriocarcinoma

- Placental site trophoblastic tumour

- Epithelioid trophoblastic tumour

Prof Michael Wells, University of Sheffield
Persistent trophoblastic disease = gestational trophoblastic neoplasia (WHO)
not a histopathological diagnosis

- $15\%$ of patients with complete mole
- $0.5\%$ of patients with partial mole
- Majority are invasive moles
- Choriocarcinoma
<table>
<thead>
<tr>
<th>FIGO RISK SCORING</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 40</td>
<td>≥ 40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td>-</td>
</tr>
<tr>
<td>Interval months from index pregnancy</td>
<td>&lt; 4</td>
<td>4 - &lt; 7</td>
<td>7 - &lt; 13</td>
<td>≥ 13</td>
</tr>
<tr>
<td>Pre-treatment serum hCG (IU/L)</td>
<td>&lt; $10^3$</td>
<td>$10^3$ - $10^4$</td>
<td>$10^4$ - $10^5$</td>
<td>≥ $10^5$</td>
</tr>
<tr>
<td>Largest tumour size (including uterus) cm</td>
<td>&lt; 3</td>
<td>3 - &lt; 5</td>
<td>≥ 5</td>
<td>-</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastro-intestinal</td>
<td>Liver, brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>-</td>
<td>1-4</td>
<td>5-8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>-</td>
<td>-</td>
<td>Single drug</td>
<td>2 or more drugs</td>
</tr>
</tbody>
</table>
hCG monitoring of GTD
Criteria for chemotherapy

- Static or rising hCG after 2nd/3rd uterine evacuation
- hCG > 20,000iu after 2nd/3rd uterine evacuation
- Persistent uterine haemorrhage with raised hCG
- Persistent elevation of hCG 6 months post-uterine evacuation
- Pulmonary metastases with static or rising hCG
Hydatidiform mole - predictive factors for PTD (GTN)

\[ \uparrow \text{telomerase activity} \]
\[ \downarrow \text{apoptotic indices (TUNEL & M30 CytoDeath antibody)} \]
\[ \uparrow Mcl-1 \text{ (anti-apoptotic gene)} \]
\[ \downarrow \text{ferritin light polypeptide & IGFBP-1} \]

Cheung \textit{et al}
Case History

27 yrs old female – sudden onset of right sided hemiparesis, headache and vomiting, 12 weeks after spontaneous miscarriage of a 24 week fetus
Histopathological findings

- Disseminated trophoblastic disease
- No choriocarcinoma in the uterus
- Normal fetus
Placental site trophoblastic tumour

- weeks to years after pregnancy
- average interval 18-30 months
- invasive uterine mass (mean - 5cms diameter)
- paternal allele present
- absence of Y chromosome
PSTT

Compared to Choriocarcinoma

- Slow growing
- Late metastases
- Lymph node involvement more common
- Less chemosensitive
- Less hCG
Placental site trophoblastic tumour factors associated with poor prognosis
(Baergen et al Gynecol Oncol 2006; 100: 511-520)

- Deep invasion
- Clear cells
- Extensive necrosis
- Mitoses+
PSTT Methods

Å Retrospective study:

- 62 patients with PSTT
- Evaluated and/or treated between 1975 and 2006 in the UK GTD service (35,550 women registered)
- Pathology centrally reviewed

# PSST Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>20-54</td>
<td></td>
</tr>
<tr>
<td><strong>Antecedent Pregnancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Mole</td>
<td>8</td>
<td>(13%)</td>
</tr>
<tr>
<td>Partial Mole</td>
<td>1</td>
<td>(2%)</td>
</tr>
<tr>
<td>Termination</td>
<td>6</td>
<td>(10%)</td>
</tr>
<tr>
<td>Miscarriage/Stillbirth</td>
<td>10</td>
<td>(16%)</td>
</tr>
<tr>
<td>Term</td>
<td>37</td>
<td>(60%)</td>
</tr>
</tbody>
</table>
PSST Presenting Symptoms

- Vag. Bleeding: 66.1%
- Abdom. Pain: 27.4%
- Ameno-rrhea: 25.8%
- Nephrot. Synd: 4.8%
- Resp. Symps: 4.8%
- Uterine rupture: 3.2%
- Neuro. Symps: 3.2%
## PSST Patient Characteristics

<table>
<thead>
<tr>
<th>Interval to Antecedent Pregnancy</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2-264</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12 months</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-47 months</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥48 months</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(24%)</td>
<td>(55%)</td>
<td>(21%)</td>
<td></td>
</tr>
</tbody>
</table>

| Disease manifestation           |                |               |               |
| No extra-uterine disease        | 36             |               | (58%)         |
| Uterine and extra-uterine, pelvic disease | 5 |               | (8%)          |
| Distant metastases              | 21             |               | (34%)         |
Diagnosis established following
- uterine evacuation (n=38, 61%),
- hysterectomy (n=19, 31%)
- or tumour biopsy (n=5, 8%).
48 months from causative pregnancy is critical

48 month cut-off

Specificity 100%
Sensitivity 93%

<table>
<thead>
<tr>
<th>Time</th>
<th>Dead</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48</td>
<td>1/49</td>
<td>98%</td>
</tr>
<tr>
<td>≥ 48</td>
<td>13/13</td>
<td>0%</td>
</tr>
</tbody>
</table>
Stage predicts survival

Follow-up (years)

Percentage Survival

P = 0.0003
Mitosis no clear cut-point

ROC Curve for Mitosis

1 - Specificity

Diagonal segments are produced by ties.
hCG no clear cut-point

ROC Curve For hCG

Sensitivity

1 - Specificity

Diagonal segments are produced by ties.
### Univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval ≥ 48 months*</td>
<td>p &lt; 0.00001</td>
</tr>
<tr>
<td>Age ≥ 36 yrs</td>
<td>p &lt; 0.00001</td>
</tr>
<tr>
<td>hCG (continuous)</td>
<td>p = 0.014</td>
</tr>
<tr>
<td>FIGO Stage</td>
<td>p = 0.0003</td>
</tr>
<tr>
<td>No of mets</td>
<td>p = 0.0002</td>
</tr>
<tr>
<td>Mitosis (continuous)</td>
<td>p = 0.008</td>
</tr>
</tbody>
</table>

*remained significant on multivariate analysis
PSTT

- FIGO risk score: not applicable
- Stage I disease: surgery is sufficient unless there are other risk factors
- Stage II, III & IV: combined surgery and chemotherapy
- Chemotherapy not as effective compared with other forms of GTD
- Why 48 months since antecedent pregnancy is the optimum discriminator for survival is unclear
Epithelioid trophoblastic tumour

- Cells resemble chorion laeve
- Nodular islands of trophoblast surrounded by extensive necrosis
- Hyaline-like matrix
- Cells smaller & less pleomorphic than PSTT
- p63 positive
C=interstitial lung expansion by cellular infiltrate

D=higher power of cellular infiltrate.

E=Cam 5.2

F=Inhibin.
Placental site nodule

- Usually incidental
- Months / years post pregnancy
- Small, well circumscribed
- Hyalinised
Placental site nodule

• single cells, clusters or cords of bland, uniform cells
• no infiltration
• no mitoses
• Ki67 < 5%
Placental site nodule transformed into a malignant epithelioid trophoblastic tumour with pelvic lymph node and lung metastasis

Tsai et al Histopathology 2008; 53: 601-604
Placental site nodule  ν  atypical placental site nodule  ν  epithelioid trophoblastic tumour

- Significant areas of necrosis
- Increased Ki-67
- Foci of calcification
- Increased Cyclin E expression
Placental site nodule v Epithelioid trophoblastic tumour

Ki-67

p63
Case history 1

• 33 yrs old female
• persistent back pain 2 months into first pregnancy
• pre-eclampsia
• normal infant delivered at 36 weeks by caesarean section
• progressive numbness and weakness affecting both lower limbs
• lower motor neuron signs with paraplegia
**Placental findings**

MACRO

A single placental disc weighing 260gms and measuring 12.2 x 11.5 x 2 cm. The maternal surface is congested and contains a crater 7 x 8 cm in maximum dimension. Slicing of the parenchyma reveals infarcted tissue in this area.

MICRO

.. in the area of crater formation established infarction is identified together with some clotted fibrin at the placental base.

COMMENT

“The overall features are compatible with sub-acute retroplacental haematoma with localized established infarction and ischaemic change...”
Case history 2

Å MRI showed a lesion at T9-10
Å laminectomy of T8-10 vertebrae with debulking of extradural tumour
Å neurological recovery
Å serum βhCG - 20,722 iu/L
Å CT scan - bilateral opacities suggesting pulmonary metastases
Case history 3

Â Initially, the biopsy of the spinal mass was reported as "CHORIOCARCINOMA"
Â the patient was referred to the Sheffield Trophoblastic Unit
Â the biopsy of the spinal mass was reviewed
Population of non-villous (intermediate trophoblast) identified in the normal term placenta between Rohr's layer of fibrinoid and Nitabuch's fibrinoid - persistent cytotrophoblast of the original cytotrophoblastic shell
inhibin
DIAGNOSIS

Intraplacental trophoblastic tumour of placental basal plate cytотrophoblast (intraplacental epithelioid trophoblastic tumour)
Case history 4

- commenced on high dose methotrexate, alternating with dactinomycin and etoposide
- after 5 courses, ßhCG was persistently marginally elevated
- regime changed to etoposide and cisplatin, alternating with etoposide and methotrexate
- resection of lung lesions
- radiotherapy to the spine
Case history 5

- fully mobile
- back in employment
- βhCG ‑ negative
- the patient has declined hysterectomy ‑ thus we will never know what (if any) residual disease was present in the uterus!
INTRAPLACENTAL EPITHELIOID TROPHOBLASTIC TUMOUR

A possibly a unique case
A clinical presentation with spinal metastases has been reported for choriocarcinoma but not for PSTT or ETT