FIRST REGIONAL EDUCATION MEETING ON GESTATIONAL TROPHOBLASTIC DISEASES October 12-14, 2018 Beijing, China
Greetings from Sheffield (来自谢菲尔德的问候)
Barry W Hancock

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Placental site (and epithelioid) trophoblastic tumours – current trends
In placental site trophoblastic tumor necrosis is often extensive but unlike choriocarcinoma hemorrhage is less conspicuous.
Placental site trophoblastic tumor infiltrating myometrium. Cells are predominantly mononuclear and mitoses are rare. Infiltration is predominantly interstitial and tumors express more hPL than hCG.
The ISSTD global placental site and epithelioid trophoblastic tumour (PSTT/ETT) database – an analysis of 325 patients

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Centres for Gestational Trophoblastic Disease, Sheffield* and London*, UK
World Series (to 2015)
(4 - 62 cases)

Feltmate et al [2001]
Kim [2003]
Hoekstra et al [2004]
Bonazzi et al [2004]
Baergen et al [2006]
Piura et al [2007]
Schmid et al [2009]
Lan et al [2010]
Chen et al [2011] ETT
Hyman et al [2013]
Moutte et al [2013]
Van Trommel et al [2013]
Zheng et al [2015]
World Literature (in 2015)

Immense variation!

- 239 cases from 13 series
- <1 - 7% of GTN
- Metastases 0 - 53%
- Survival 57 - 100%
- Poor prognosis $\geq$ Stage 2, $>$time since antecedent pregnancy, (>mitosis, lymph node involvement, clear cytoplasm)
- ETT is sometimes categorised together with PSTT
Placental Site Trophoblastic Tumour Database Project 2006-2016
Contributors

- New England Trophoblastic Disease Center, Boston, US
- Centre Français des Maladies Trophoblastiques, Lyon, France
- Nijmegen, the Netherlands
- Zhejiang University, Hangzhou, China
- Registre des Maladies Trophoblastiques du Québec, Canada
- Peking Union Medical College, China
- Aarhus Universitetshospital, Denmark
- Queensland Trophoblast Centre, Australia
- UP College of Medicine, Philippines
- St. James's Hospital, Ireland
- Queen Mary Hospital, Hong Kong
- Karolinska University Hospital, Sweden
- Fudan University, Shanghai, China,
- Juravinski Cancer Centre, Hamilton, Canada
- Belgrade, Serbia
- Gestational Trophoblastic Disease Centre, London, UK
- Gestational Trophoblastic Disease Centre, Sheffield, UK
The database

• 325 patients
• Data completeness variable
• Data interpreted and cleansed by UK-based team
• Histology relies on contributor’s confirmation of expert review
• Primary treatment philosophy variable
• Univariate analysis
• Multivariate analysis
275 cases were PSTT
Uni-variate analysis – many inter-dependent adverse factors

- Age at presentation > 40 years \( p < 0.001 \)
- Live birth \( p < 0.01 \)
- Interval from pregnancy > 4 years \( p < 0.0001 \)
- FIGO stage ≥ 2 \( p < 0.001 \)
- FIGO high-risk score \( p < 0.0001 \)
- Serum hCG > 10,000 \( p < 0.01 \)
- Tumour size >3cm \( p < 0.0001 \)
- Lympho-vascular invasion \( p < 0.001 \)
- Outer half myometrial invasion \( p < 0.01 \)
- Serosal invasion \( p < 0.005 \)
- Chemotherapy (not adjuvant) \( p < 0.0001 \)
Other factors evaluated

- Gender of antecedent pregnancy  ✗
- Mitosis ✓ p=0.05
- hCG/hPL staining  ✗
- Treating centre ✓
- Primary surgery ✓
- Primary response CR vs PR/NR ✓
- Distant metastasis other than to lungs ✓
- PSTT vs ETT ✗

We did not assess tumour necrosis
135 cases had surgery alone.
Treatment

- 135 (41.4%) Stage 1 had surgery alone (mortality 3.4%)

- 60 (18.7%) had surgery/adjuvant chemotherapy (mortality 3.0%)

- Stage 1 with surgery +/- chemotherapy much more likely to survive ($p < 0.0001$)

- Adjuvant chemotherapy does not add to survival for Stage 1 disease ($p = 1.000$)
Multivariate Analysis

• **Time since antecedent pregnancy**
  > 48 months vs. \( \leq \) 48 months
  HR (95% CI) 10.78 (2.12 - 54.73)
  \( p \)-value 0.004

• **FIGO Stage**
  Stage 4 vs. others
  HR (95% CI) 18.74 (3.01 – 116.63)
  \( p \)-value 0.002
Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival Probability

Disease-Free Survival Time

Months

Logrank p < .0001

Censored
Product-Limit Survival Estimates
With Number of Subjects at Risk

Disease-Free Survival Time

Survival Probability

Stage 1
Stage 2
Stage 3
Stage 4

figo_stg
Logrank p < .0001
+ Censored
Product-Limit Survival Estimates
With Number of Subjects at Risk

0.00 0.25 0.50 0.75 1.00

Disease-Free Survival Time

Stage 1 185 21 8 1 0
Stage 2 19 1 0
Stage 3 56 8 2 0
Stage 4 18 1 0

0 10 20 30 40

figo_stg  Stage 1  Stage 2  Stage 3  Stage 4
Conclusions

• This is the largest descriptive dataset for PSTT/ETT and affirms the prognostic importance of stage and interval from antecedent pregnancy

• ETT is not PSTT but management can be similar

• We suggest the following stage-adapted therapy:
  1) Stage 1 with no adverse other factors – surgery alone
  2) Stage 1 with adverse factors – surgery with adjuvant chemotherapy
  3) All others – intensive chemotherapy +/- surgery.
An analysis of the clinical and pathological manifestations of 108 patients with PSTT registered in two Gestational Trophoblastic Disease (GTD) Centers and six tertiary hospitals located in six different provinces in China.

Univariate analysis revealed the interval (36 M) between antecedent pregnancy and onset of PSTT, stage, prognostic score, and necrosis as significant predictors of poor survival but only stage remained significant on multivariate analysis.
This result indicates that stage is the key prognostic factor for PSTT survival (P = 0.003).
Conclusion

• Patients with FIGO stage IV disease demonstrate the most critical risk indicator of PSTT in the current study.

• Surgery without chemotherapy is recommended as first line treatment for patients with stage I who are at low-risk.

• Preservation of fertility is considered in highly-selected patients with localized tumor
Prognostic factors and optimal management of placental-site and epithelioid trophoblastic tumors advocating an aggressive treatment approach for high-risk patients

F. Froeling et al, for the UK Gestational Trophoblastic Service

Using the world’s largest national data set to eliminate case ascertainment bias, we identify prognostic factors and assess whether the introduction of a new treatment approach for poor prognosis patients has increased survival.

Two cohorts 1973-2006 (old) and 2007-2014 (new)
Survival by stage

HR 4.54 (1.25-16.58)
p=0.022
Survival by time since antecedent pregnancy

HR 30.61 (5.48-170.95)
P<0.0001
Survival for all patients - old v new cohorts
Survival for first and second patient cohort patients (antecedent pregnancy $\geq 48$ months)
Conclusion

PSTT/ETT carries a good prognosis but patients presenting with stage IV disease or more than 4 years from their last known pregnancy have poorer outcomes and should be considered for more aggressive, platinum-based and novel therapeutic approaches.
There may well be a difference in the nature of patients treated since the reported incidence of PSTT in the Chinese cohort of patients was significantly higher at 3% versus 0.2% in the UK with a relatively low overall mortality rate of just 6.5% compared to 19% in the UK

- a difference in genetic background
- case ascertainment bias
- small sample sizes, and/or
- variances in therapies
Forty-five patients with ETT and 9 patients with PSTT/ETT, from the ISSTD database, were studied.
Survival according to time since pregnancy
Survival according to Stage
Conclusion

- ETT is a potentially high-risk trophoblastic neoplasm especially in patients with high stage disease and a treatment interval more than 48 months since the antecedent pregnancy.
- Surgery seems adequate for low stage disease.
- High stage disease requires a combination of treatment modalities and should be treated in a centre with experience in GTN.
For Discussion

• Can we all agree to abide by stage-adapted ‘guidelines’?

• Can ETT be managed like PSTT?

• What is the role for high dose chemotherapy?

• What is the role for fertility conservation?

• Can we agree to collect more data (particularly prospectively) and to seek follow-up details?
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  NEEDS ENTHUSIASM
The international PSTT/ETT/UHR database
(http://stdc.group.shef.ac.uk/psttuhr/)
Thank you for listening (感谢您的收听)