ESO Course "Rare female genital cancers"

Atypical Placental Site Nodule, Placenta Site Trophoblastic Tumor AND Epitheloid Trophoblastic Tumor

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What is the incidence of APSN, PSTT and ETT?

Are APSN, PSTT and ETT rare diseases?

What are the challenges for rare diseases?

Can FIGO scoring be used to predict treatment of PSTT and ETT?

How can PSTT and ETT be distinguished?

Can fertility be preserved?

APSN, PSTT, ETT

WHO definition of rare disease: affected people < 1 in 2000

ERN: affected people < 6 in 100,000

Questions & Challenges for both doctors and patients

Table 1
Average frequency and incidence of individual entities of GTD, 1994–2013.

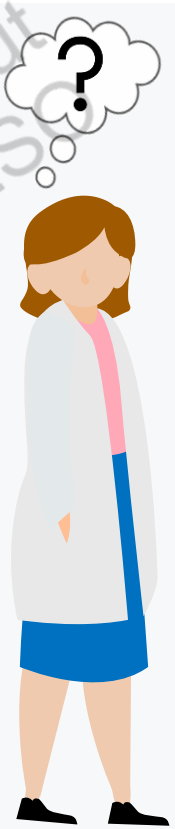
GTD diagnosis	Number	Percentage	Incidence[a]
Complete hydatidiform mole	1993	31.4	0.52
Partial hydatidiform mole	2548	40.2	0.67
Invasive mole	18	0.3	0.01
Unspecified mole	594	9.4	0.16
Abortion or mole	449	7.1	0.12
Choriocarcinoma	121	1.9	0.03
Placental site trophoblastic tumor	36	0.6	0.01
Epithelioid trophoblastic tumor	4	0.1	0.00
Exaggerated placental site reaction	272	4.3	0.07
Placental site nodule	306	4.8	0.08
Total	6341	100	1.66

[a] Incidence per 1000 deliveries.

Eysbouts et al. 2016 (Incidence in the Netherlands 1994-2013)

Table 1. Challenges of rare gynaecologic cancers for healthcare professionals

Small number of patients
Scattering across a country
Fragmented knowledge
Limited validated diagnostics and treatments
Limited expertise and expert centres
No evidence based protocols
No possibility for large trials
Difficulties in obtaining funding



Slow progress in science and improvement survival

The challenge of treating and investigating rare gynaecologic cancers. Lok C, Amant F. Curr Opin Oncol. 2021 Sep 1;33(5):432-434.

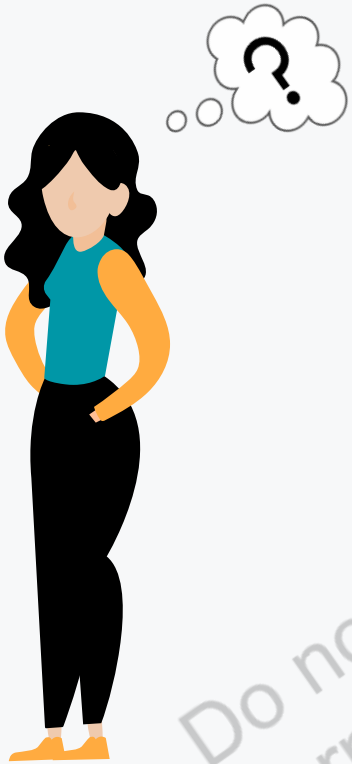
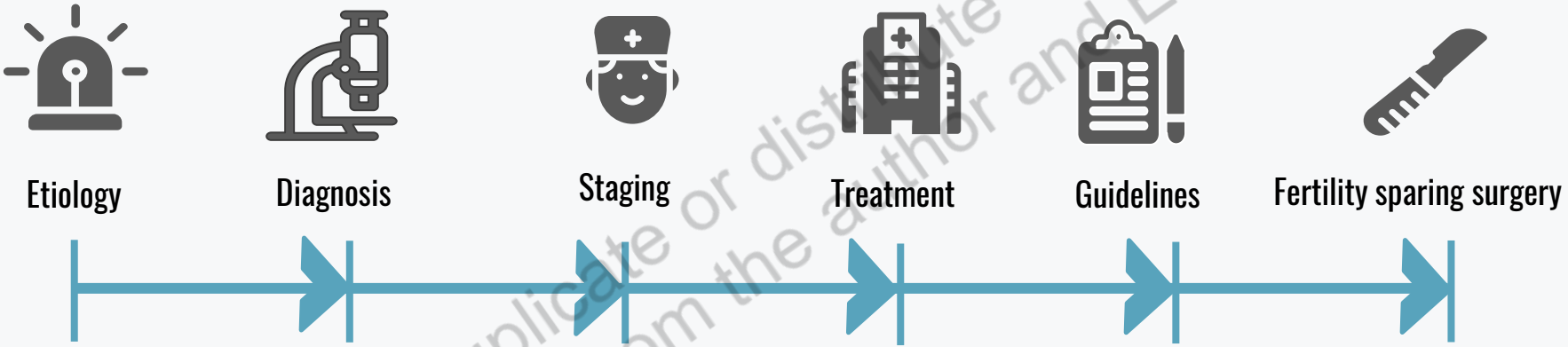


Table 2. Challenges of rare gynaecologic cancers for patients

More uncertainty on treatment
Less available patient information
Only standard leaflets available
Change to meet a physician that has never seen the cancer before
Change to receive different advices in different hospitals
Smaller change to get in contact with fellow sufferer

The challenge of treating and investigating rare gynaecologic cancers.
Lok C, Amant F. Curr Opin Oncol. 2021 Sep 1;33(5):432-434.



Trophoblast: “Tree”

- **Trunk** →intermediate trophoblast

- **Leaves** → Syncytiotrophoblast & Cytotrophoblast

Hydatidiform mole
Choriocarcinoma

Bron: https://dalalounatuurlijk.nl/

Source: https://dalalounatuurlijk.nl

Trophoblast: “Tree”

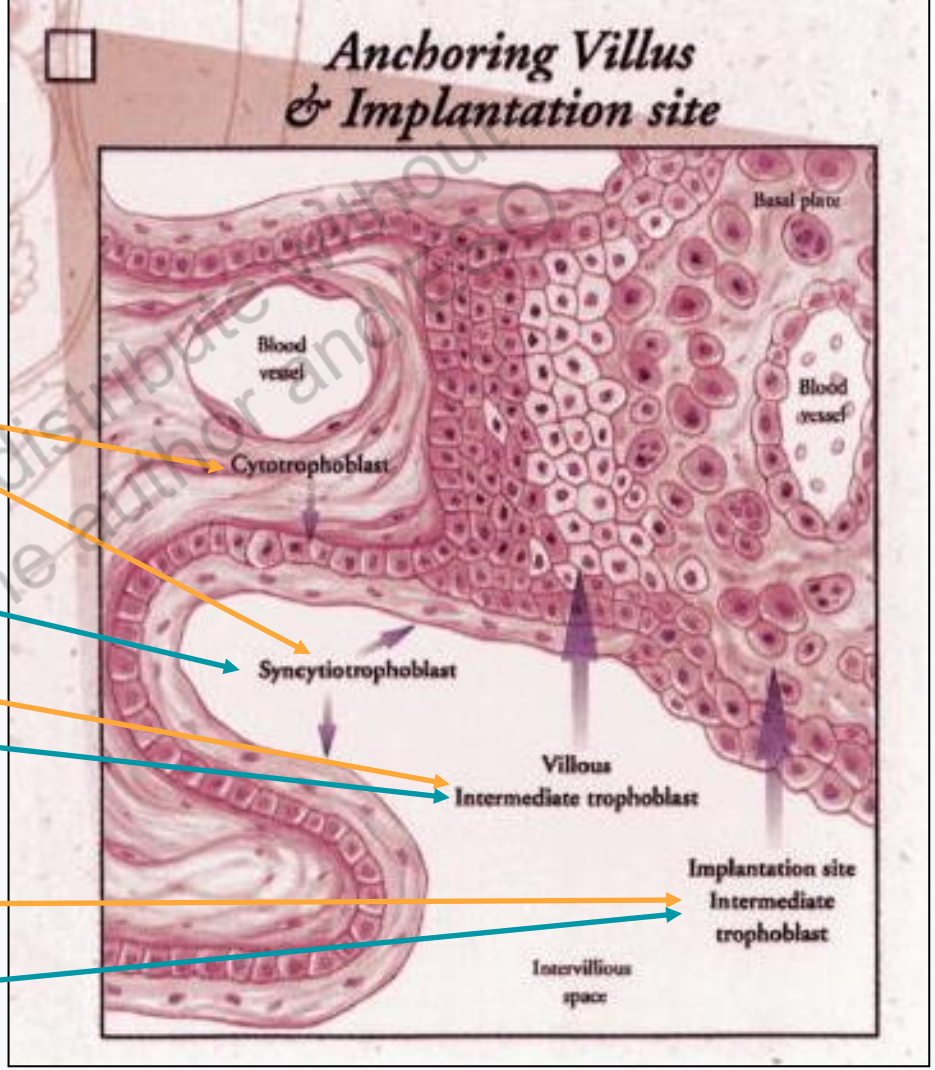
- Trunk:
  - Implantation site intermediate trophoblast
    - Exaggerated placental site (EPS)
    - Placental site trophoblastic tumor (PSTT)
  - Villous intermediate trophoblast
    - (Atypical) Placental site nodule (PSN)
    - Epitheloid trophoblastic tumor (ETT)

Benign and **malignant** trophoblastic tumors

- Complete/partial hydatidiform mole
- Choriocarcinoom

- Placental site nodule (PSN)
- Epitheloid trophoblastic tumor (ETT)

- Exaggerated placental site (EPS)
- Placental site trophoblastic tumor (PSTT)

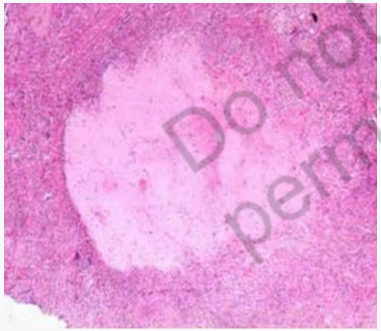


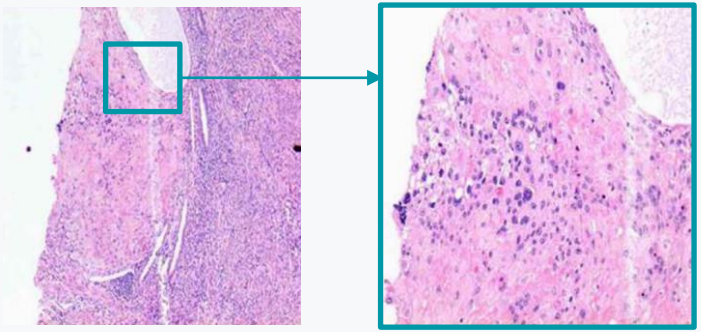
Typical PSN

- PSN morphologically appear as small (<4 mm), wellcircumscribed endometrial nodules composed of intermediate trophoblast of chorionic type
- Central hyalinization
- Usually incidental findings at hysterectomy or in biopsy specimens of endometrium,
- Lower uterine segment, and cervix, with rare cases occurring in the fallopian tube, broad ligament, and ovary

APSN

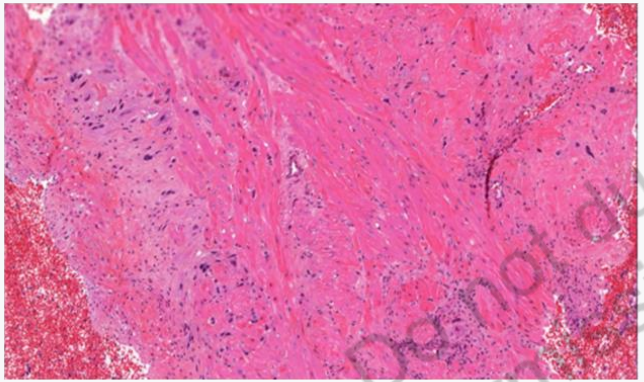
- Histopathologic features intermediate between typical PSN and PSTT/ETT
- Usually larger in size than typical PSN
- Have increased cellularity with more cohesive nests and cords of cells, mild cytologic and/or nuclear atypia, and presence of mitosis, necrosis, and/or a raised proliferation index (Ki-67)
- Subjective
- Not included in WHO classification





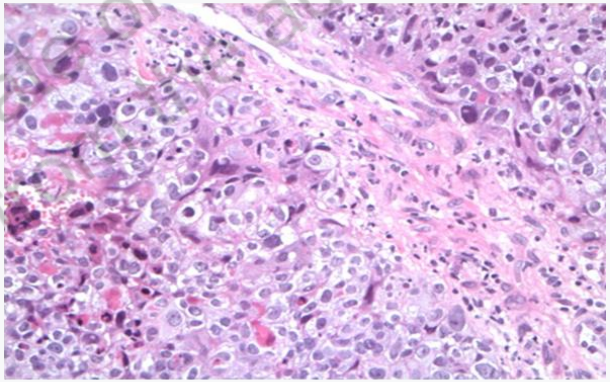
H&E

PSTT

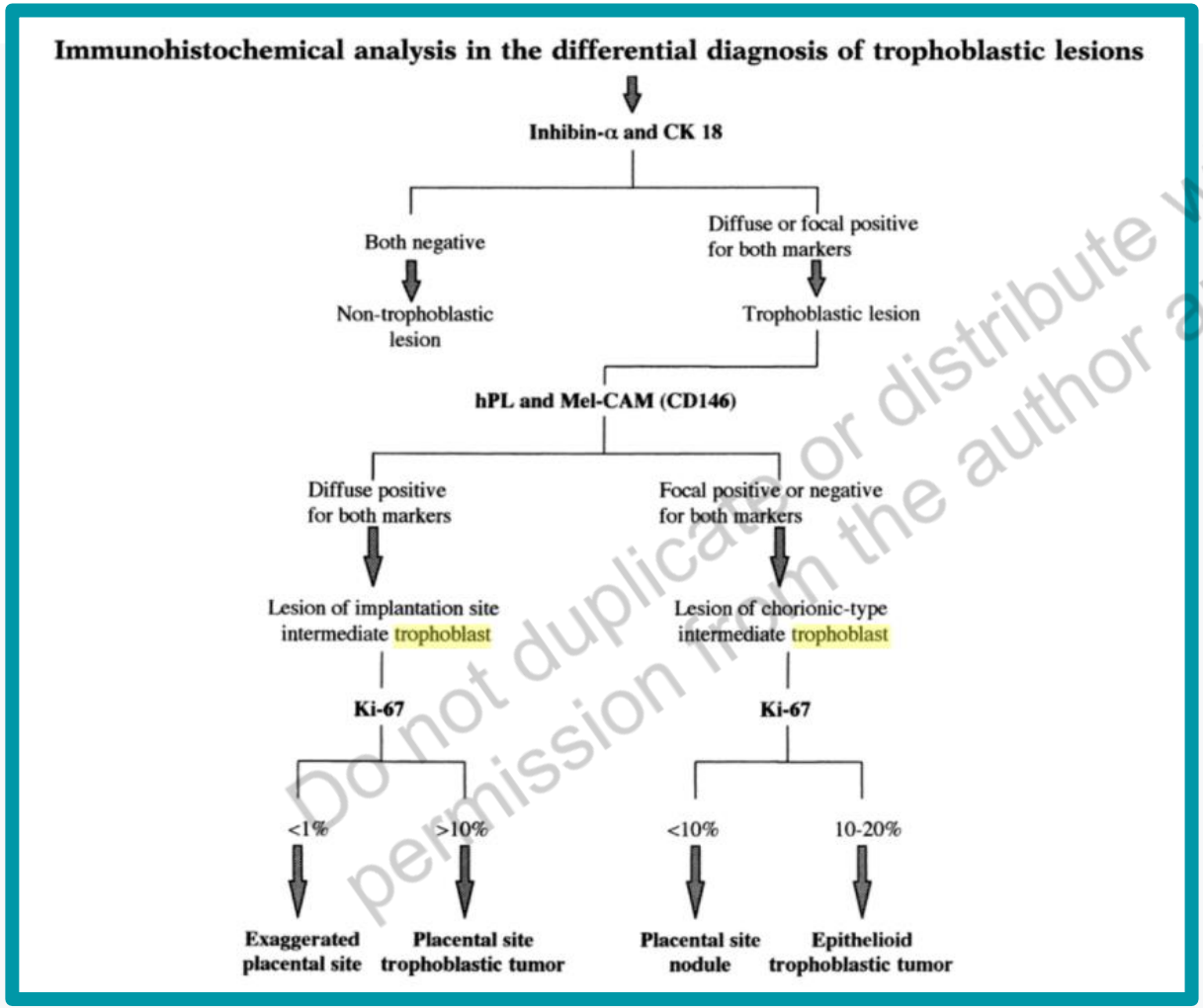


Tumor “breaks” myometrium

ETT



Pale cytoplasm, nuclear atypia, necrosis



Blaustein, 6e editie

1	Disease confined to the uterus
2	GTN extends outside of the uterus, but is limited to the genital structures adnexa, vagina, broad ligament
3	GTN extends to the lungs, with or without known genital tract involvement
4	All other metastatic sites

FIGO SCORING	0	1	2	4
Age	< 40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4 – <7	7 – <13	≥ 13
Pre-treatment serum hCG (IU/L)	$<10^3$	10^3 – 10^4	10^4 – $<10^5$	≥ 10^5
Largest tumor size (including uterus) cm	<3	3 – <5	≥ 5	-
Site of metastases	Lung	Spleen, Kidney	Gastro-intestinal	Liver, Brain
Number of metastases	-	1 – 4	5 – 8	> 8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

FIGO score not suitable to predict clinical course of PSTT & ETT

Not many cases reported worldwide (series of Kaur, n=21)

Clinical presentation:

- Mean age 35 years (28-43 years)
- Irregular vaginal blood loss (70%)
- No raised serum hCG (unless transformation to PSTT/ETT with metastases)
- recurrent pregnancy loss
- abnormal cervical smear
- most behaving in a benign manner
- **malignant GTD was associated in 3/21 (14%) cases of APSN, either concurrently or developing within 16 months of APSN diagnosis**
- clinical significance remains uncertain, differentiation with PSTT and ETT difficult

Kaur et al, International Journal of Gynecological Pathology 2015, 34:152–158

Around 700+ cases worldwide reported

Clinical presentation:

- **Irregular vaginal blood loss (31-79%)**
- **Amenorroea: (11-43%)**
- **Persistent increased hCG (7%)**
- **70% early stage at presentation**
- **Most frequent hematogeneous metastases (lung 10-29%)**

Gadducci, gynecol oncol 2019

Around 100+ cases worldwide reported

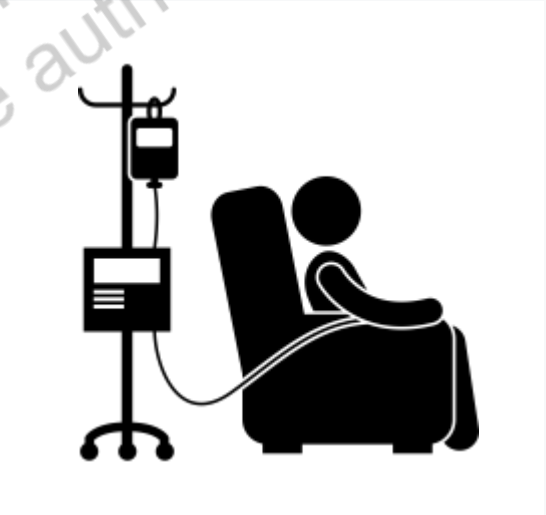
Clinical presentation:

- Irregular vaginal blood loss (57-67%)
- Localization:
  - Uterus: 40%
  - Cervix: 30%
- 58-75% early stage at presentation

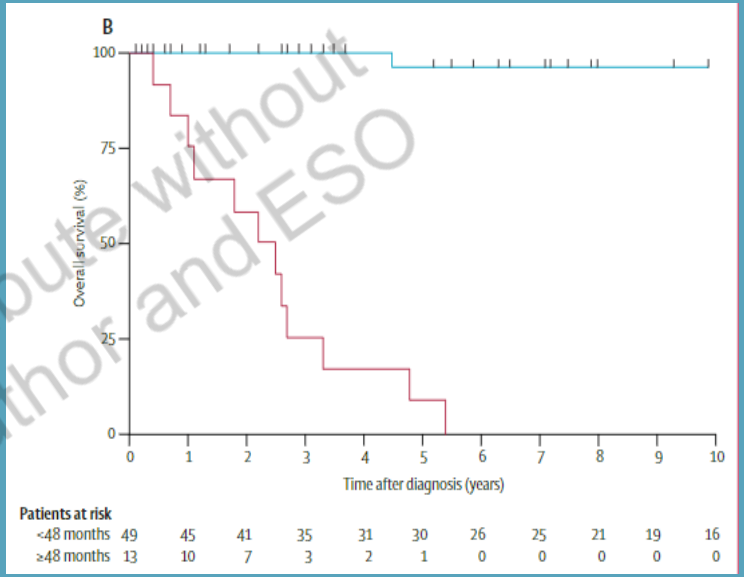
Treatment

Surgery

Chemotherapy

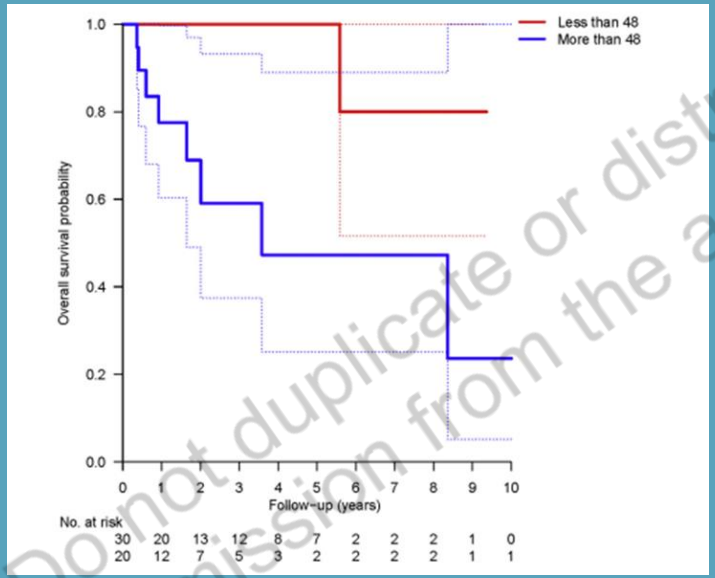


Why is interval important for treatment?



PSTT, Schmid 2009, N=62

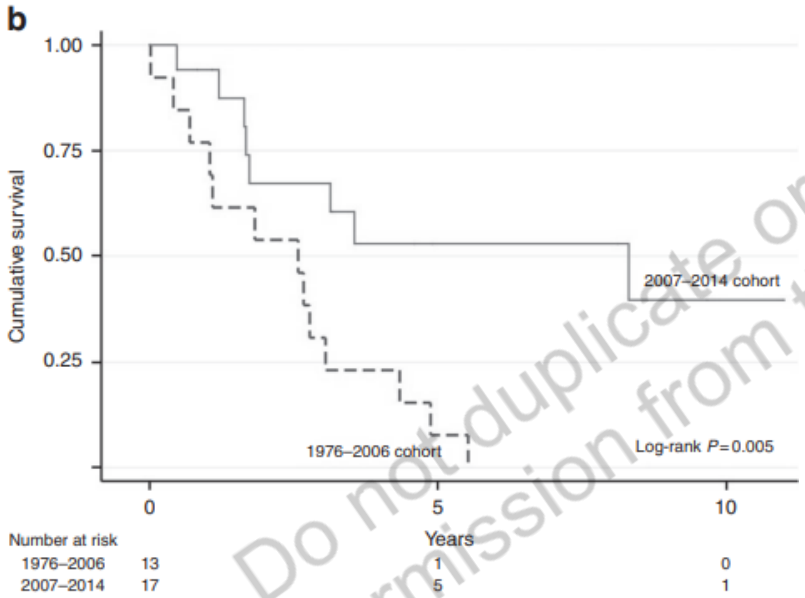
ETT, Frijstein 2019, N=54



Interval good predictor of poor prognosis of disease

Frijstein et al. Gynecol Oncol 2019 Feb;152(2):361-367

Rationale for adjuvant chemotherapy after interval >48 months



- PSTT & ETT, Froeling 2019
- Prognostic variabels OS: stage and **interval**
- Since adjuvant chemotherapy was added in patients with interval >48 months, increase OS
- No RCT
- N=125

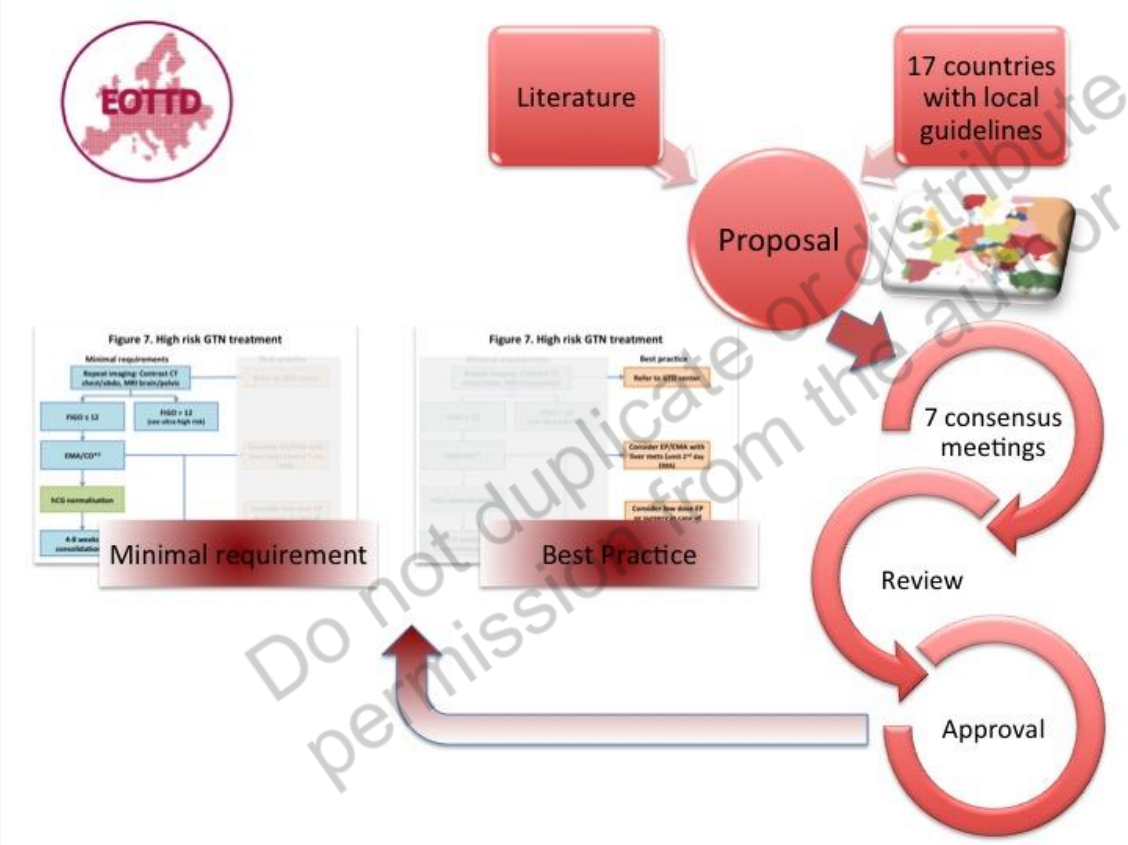
Froeling et al. 2019 Mar;120(6):587-594

Table 3. Solutions to deal with rare gynaecologic cancers

Collecting widespread data: registration & classification
Sharing knowledge
Guideline development
Development of research models:
translational models
adjusted clinical trials for small populations
Biobanking
National networks
International networks
Improving infrastructure
Emphasizing importance to funding agencies

The challenge of treating and investigating rare gynaecologic cancers. Lok C, Amant F. Curr Opin Oncol. 2021 Sep 1;33(5):432-434.

Practical clinical guidelines of the EOTTD for the treatment and referral of GTD



Guidelines

European Journal of Cancer 130 (2020) 228–240

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease

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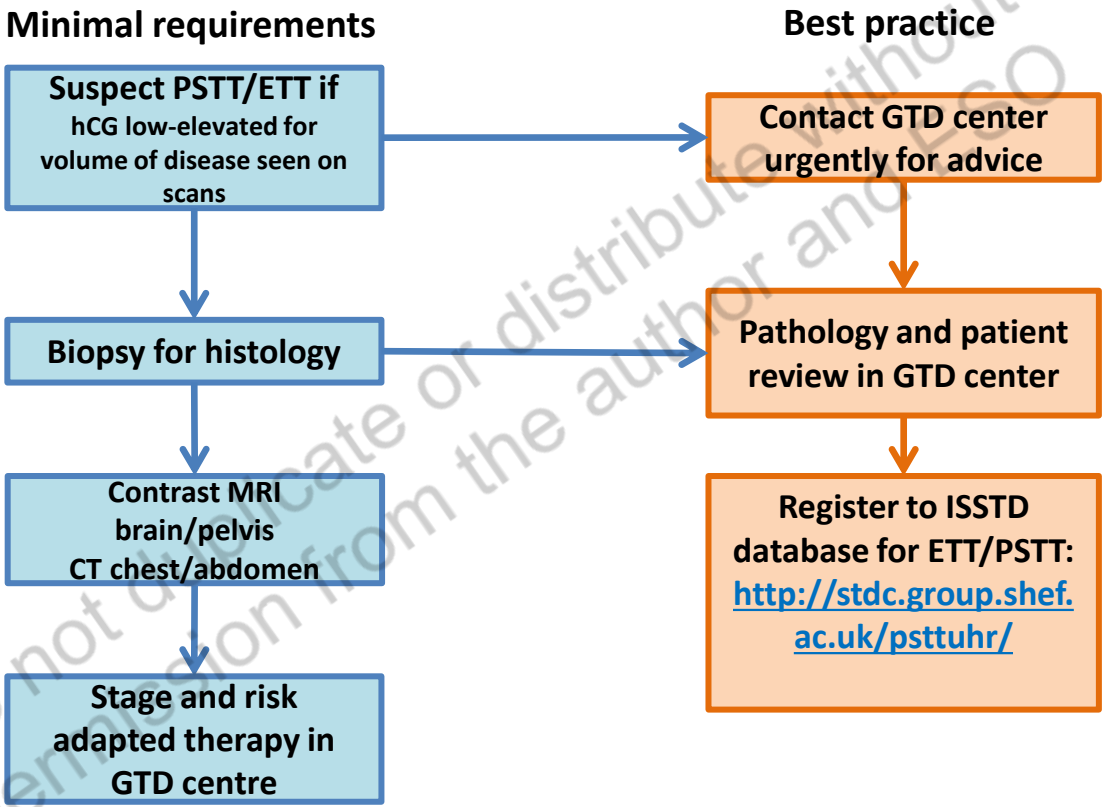
Diagnosis PSTT/ETT



Lok & van Trommel, Practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease, EJC 2020

Treatment PSTT/ETT

Minimal requirements

Stage I

Antecedent pregnancy < 48 months
- Hysterectomy + surveillance

Antecedent pregnancy ≥ 48 months
- Hysterectomy + platinum based combination chemotherapy (eg EP/EMA) + surveillance
- Consider HDC or other experimental treatment

Stage II, III

Antecedent pregnancy < 48 months
- Hysterectomy + platinum based combination chemotherapy (eg EP/EMA) + resection of any visible residual disease post chemotherapy + surveillance

Antecedent pregnancy ≥ 48 months
- Hysterectomy + platinum based combination chemotherapy (eg EP/EMA) + resection of any visible residual disease post chemotherapy + surveillance
- Consider HDC or other experimental treatment

Stage IV

Antecedent pregnancy < or ≥ 48 months
- Hysterectomy + platinum based combination chemotherapy (eg EP/EMA) + resection of any visible residual disease post chemotherapy + surveillance
- Consider HDC or other experimental treatment

Best practice

- **Free surgical margins are essential**
- **Consider salpingectomy (to obtain free surgical margins)**
- **Radical hysterectomy dependent on localization of tumor**
- **Laparoscopic approach in selected cases**
- **Suspicious lymph nodes should be removed**
- **Genetics to prove gestational origin and from which prior pregnancy**
- **Order of treatment can be different in higher stage**

- **Fertility sparing surgery is experimental**

Lok & van Trommel, Practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease, EJC 2020

Author	Method	Patients	Fertility-sparing treatment	Type of fertility-sparing procedure	Maternal outcomes	Fertility outcomes
Bonazzi et al	Retrospective cohort	PSTT n=1	Hysteroscopic resection n=1		ND	ND
Zhang et al	Literature review	PSTT n=2	Chemotherapy		ND	ND
Taylor et al	Case report	PSTT n=1	Hysteroscopic resection		ND	Salvage hysterectomy
Imamura et al	Case report	ETT n=1	Laparotomic resection		Additional chemotherapy No recurrence	ND
Renaud et al	Case report	PSTT n=2	D&C		ND	Salvage hysterectomy
Tse et al	Case report	ETT n=1	Laparotomic resection		ND	Live birth n=2
Zhao et al		PSTT n=23	Chemotherapy n=20		Death n=1 Partial response n=1	Live birth n=7 (which group?)
			Laparotomic resection n=2		ND	ND
			D&C n=1		ND	ND
Chiofalo et al	Systematic review nine studies	PSTT n=18	Open procedure n=11	Laparotomic resection n=7	Additional chemotherapy n=3	Salvage hysterectomy n=5
				Modified Strassman procedure n=4	ND	ND
			Minimally invasive approach n=6	D&C Hysteroscopic resection	ND	ND
			Chemotherapy only n=1		ND	Live birth n=1
Zhang et al	Literature review and case report	PSTT n=42 ETT n=19 Mixed PSTT/ETT n=1	Local resection n=10		Additional chemotherapy n=10 No recurrence n=7 ND n=3	Live birth n=2
Alexander et al	Case report	PSTT n=13	Hysteroscopic resection n=1		No recurrence	ND

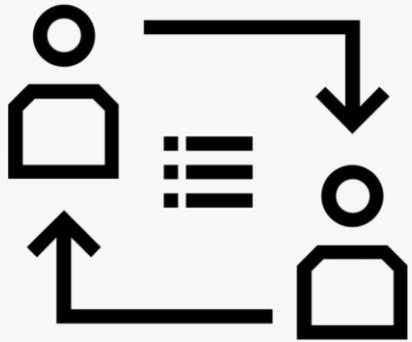
Mortality: N=1
Recurrence: N=?

Live births: N=16

Joneborg, Coopmans, van Trommel, Seckl & Lok, IJGC, 2020

Follow up PSTT / ETT

- No data about best follow up schedule
- hCG (if increased before treatment):
  - 6 weeks after normalisation
  - Monthly during 12 months
- Imaging: upon indication/according to GTD center
- Total follow-up: often 10 years is advised, certainly for higher stages



APSN

- Intermediate trophoblast
- Can develop into PSTT/ETT (10-15%)
- hCG not elevated
- Objective criteria for diagnosis still lacking
- Fertility sparing often (temporarily) possible
- Hysterectomy after fulfilling childwish
- No consensus yet on follow up

PSTT

- Intermediate trophoblast
- Incidence: 0.1/1000 pregnancies
- Prognostic factors stage and interval > 48 months
- Surgery is cornerstone of treatment
- Fertility sparing surgery in highly selected cases
- Registration in worworldwide database
- Low hCG
- Often stage I

ETT

- Intermediate trophoblast
- Incidence: 0.01/1000 pregnancies
- Prognostic factors stage and interval > 48 months
- Registration in worldwide database
- Differential diagnosis with cervical cancer
- Often lower part uterus
- Fertility sparing surgery not advised
- Low hCG
- Often stage 1

Take Home Messages

APSN, PSTT & ETT are very rare

Diagnosis can be complicated

Treatment in GTD center should be considered

EOTTD guidelines can help with management

Registration: http://stdc.group.shef.ac.uk/psttuhr/

Questions?

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