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ESMO Clinical Practice Guidelines

Gestational Trophoblastic Disease

Clinical Case Presentation

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Disclosures no potential conflicts of interest

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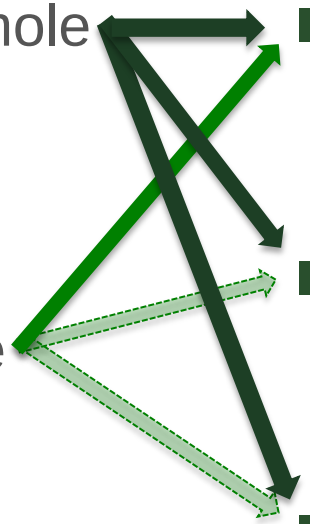
Gestational trophoblastic disease

Pre-malignant

- Complete hydatidiform mole (CHM)
- Partial hydatidiform mole (PHM)
- Atypical placental site nodule



Malignant

- Invasive mole
- Choriocarcinoma
- Placental site trophoblastic tumours (PSTT) or epitheloid trophoblastic tumour (ETT)

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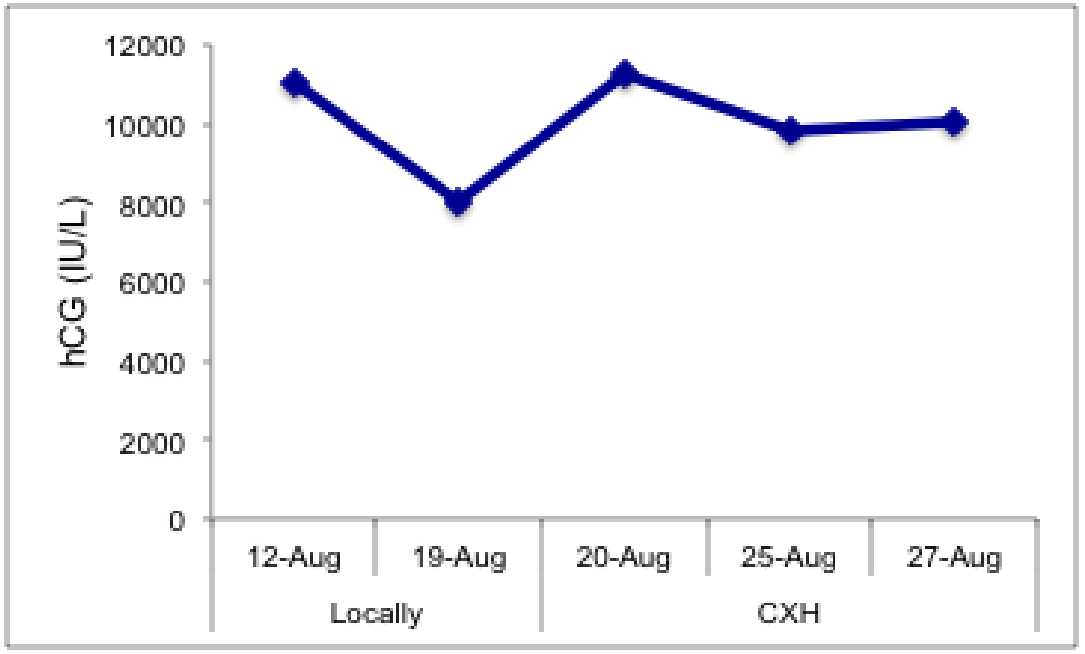
Case presentation

- 33 year old, 1st gestation
- Vaginal bleeding
- Ultrasound scan (USS) confirmed missed miscarriage
- Suction dilation and curettage (D&C)
- Histology: PHM
- hCG: ~ 10 000 IU/L



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Q 1: When to start treatment?

1. Heavy vaginal bleeding
2. Raised hCG 6 months after evacuation (even if still falling)
3. Histological diagnosis of choriocarcinoma
4. Plateaued or rising hCG after evacuation
5. Answer 1, 3 and 4
6. All of the above

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When to start treatment

1. Heavy vaginal bleeding
2. Raised hCG 6 months after evacuation (even if still falling)
3. Histological diagnosis of choriocarcinoma
4. Plateaued or rising hCG after evacuation
5. **Answer 1, 3 and 4**
6. All of the above

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Q 2: Which investigations?

1. Pelvic Doppler USS, CT chest/abdo and MRI pelvis
2. Pelvic Doppler USS and CXR; if lung lesions >1cm a CT chest/abdo
3. Pelvic Doppler USS and CXR; if lung lesions >1cm a CT chest/abdo and MRI brain
4. Pelvic Doppler USS and CXR; if lung lesions >1cm a PET-CT

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Investigations

1. Pelvic Doppler USS, CT chest/abdo and MRI pelvis
2. Pelvic Doppler USS and CXR; if lung lesions >1cm a CT chest/abdo
3. **Pelvic Doppler USS and CXR; if lung lesions >1cm a CT chest/abdo and MRI brain**
4. Pelvic Doppler USS and CXR; if lung lesions >1cm a PET-CT

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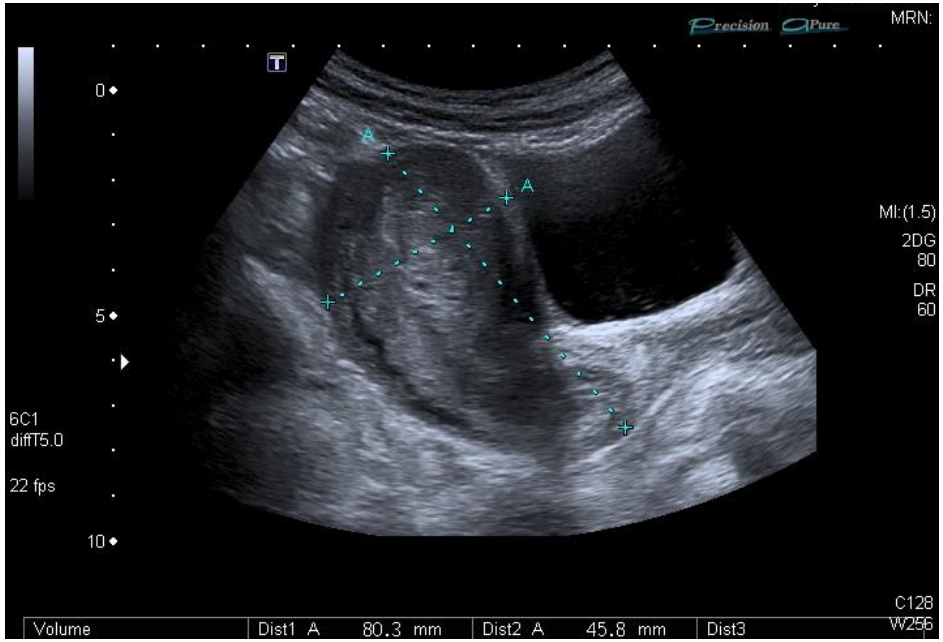
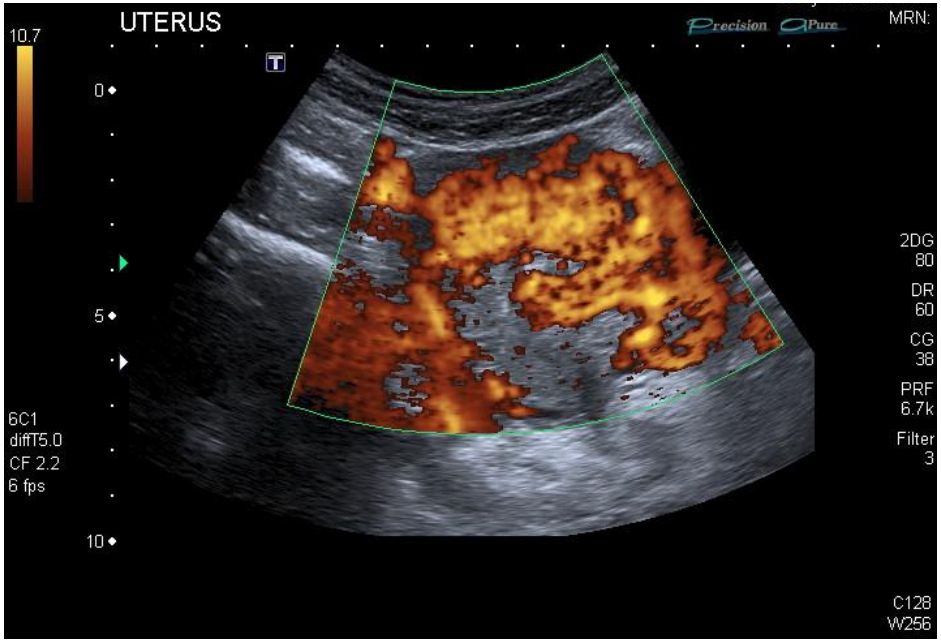
Case presentation





- 4.1 cm vascular mass in the anterior body of the uterus within the endometrial cavity
- Normal CXR
- hCG: 10 071 IU/L

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Q 3: Which treatment?

1. Second D&C
2. Methotrexate 50 mg im d1,3,5,7 alternating with folinic acid 15mg po d2,4,6,8 (MTX/FA) every two weeks
3. Capecitabine 1250mg/m2 orally twice daily for two weeks repeated every 3 weeks
4. Combination regimen with MTX, ActD and folinic acid (MFA)
5. Low dose induction chemo with etoposide 100mg/m2 and cisplatin 20mg/m2 d1and 2 before EMA/CO
6. Etoposide methotrexate + actinomycin D alternating wkly with cyclophosphamide + vincristine (EMA/CO)

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Treatment

1. Second D&C
2. **Methotrexate 50 mg im d1,3,5,7 alternating with folinic acid 15mg po d2,4,6,8 (MTX/FA) every two weeks**
3. Capecitabine 1250mg/m2 orally twice daily for two weeks repeated every 3 weeks
4. Combination regimen with MTX, ActD and folinic acid (MFA)
5. Low dose induction chemo with etoposide 100mg/m2 and cisplatin 20mg/m2 d1and 2 before EMA/CO
6. Etoposide methotrexate + actinomycin D alternating wkly with cyclophosphamide + vincristine (EMA/CO)

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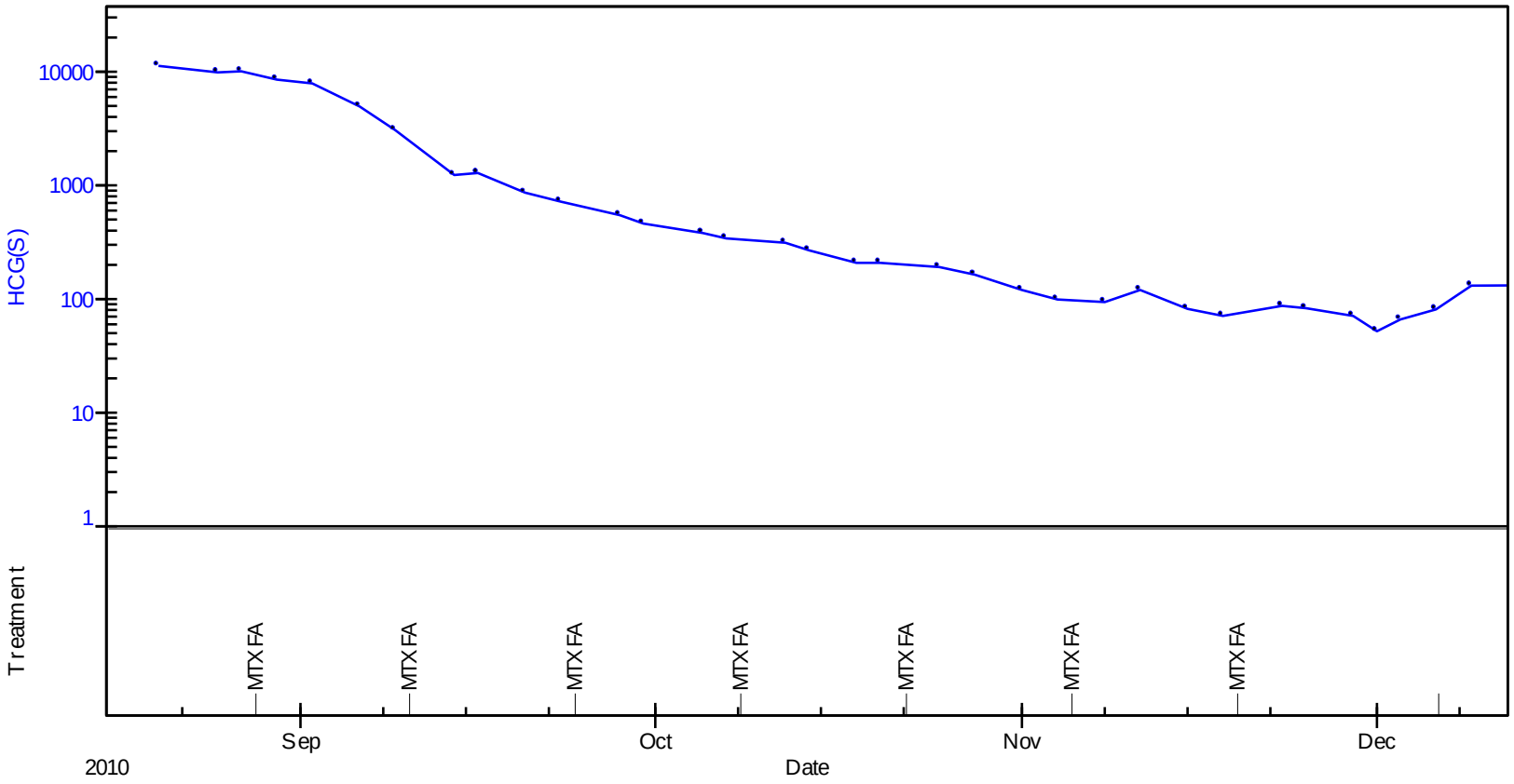
Treatment for low-risk disease started but…

- MTX 50 mg im on D1, D3, D5 and D7
- Folinic acid 15 mg 30 h after each injection of MTX
- Cycles repeated every 2 weeks



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Q 4: Next line of treatment?

1. Change to EMA/CO
2. Combination regimen with MTX, ActD and folinic acid (MFA)
3. Combination therapy with MTX, ActD and cyclophosphamide (MAC)
4. Continue single agent therapy but change to ActD

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Next line of treatment

1. Change to EMA/CO
2. Combination regimen with MTX, ActD and folinic acid (MFA)
3. Combination therapy with MTX, ActD and cyclophosphamide (MAC)
4. **Continue single agent therapy but change to ActD**

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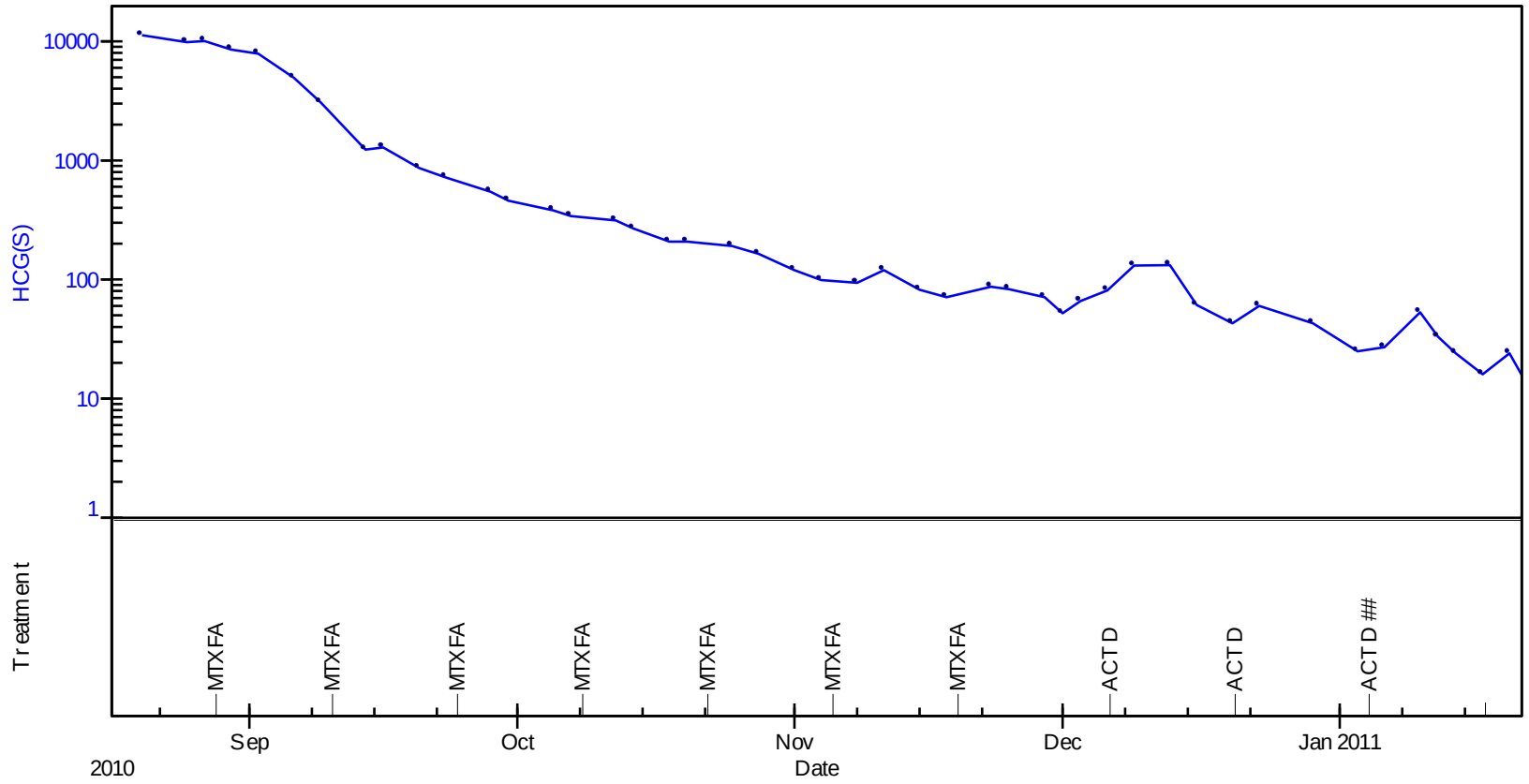
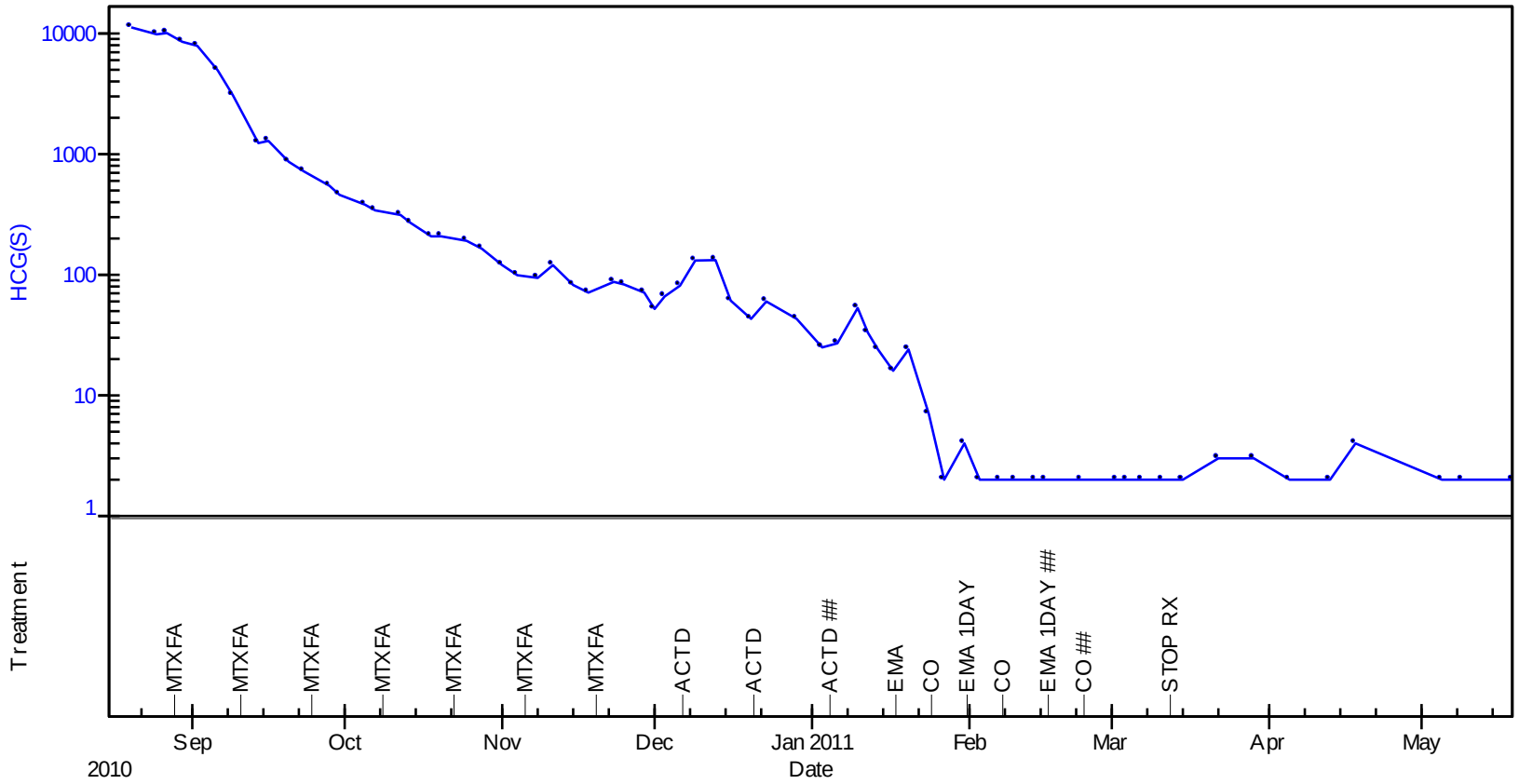
hCG < 300 IU/L and started ActD

- Actinomycin D 1.25 mg/m^2



hCG normalised with high-risk treatment EMA/CO



- Once hCG is normal: 6 weeks consolidation treatment

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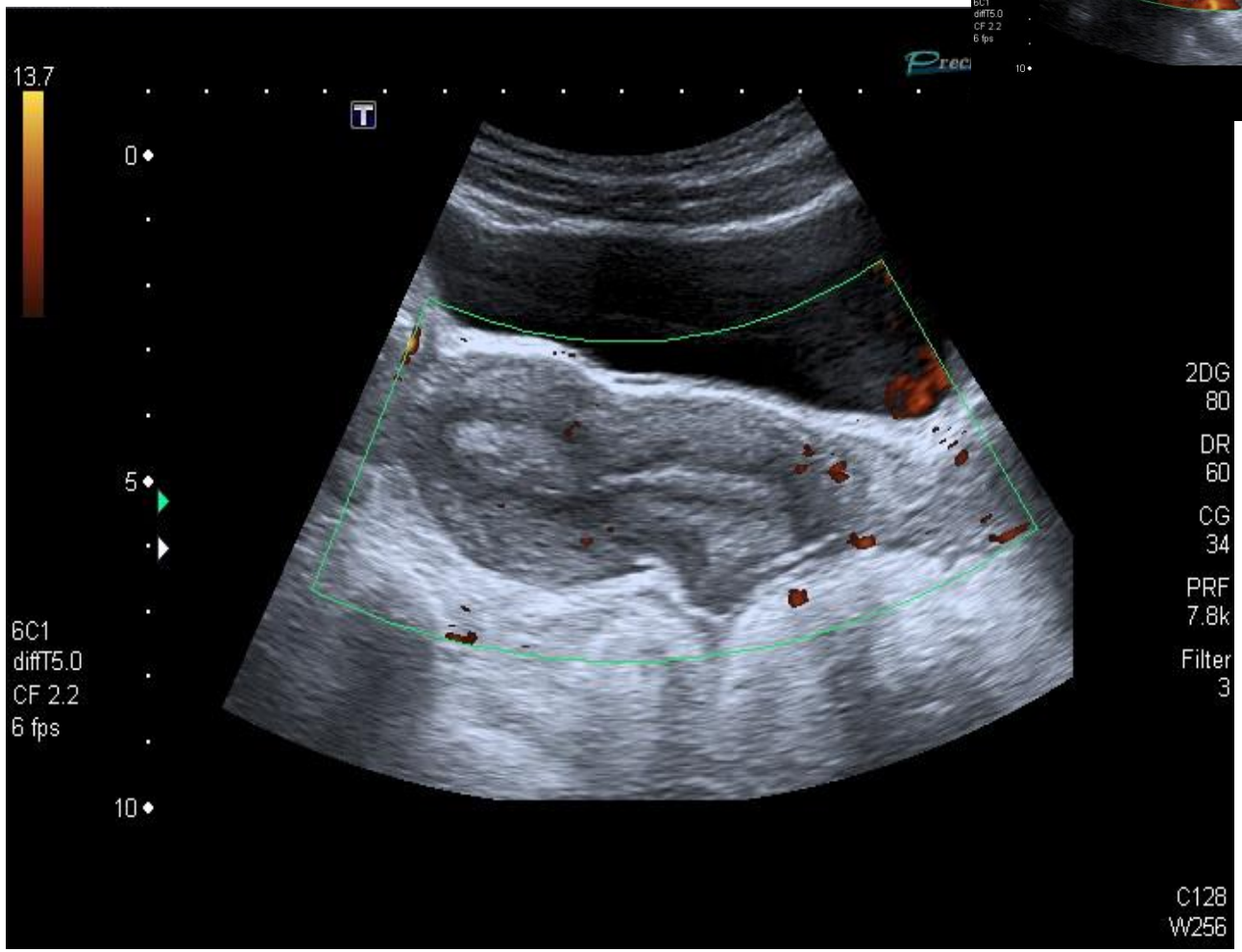
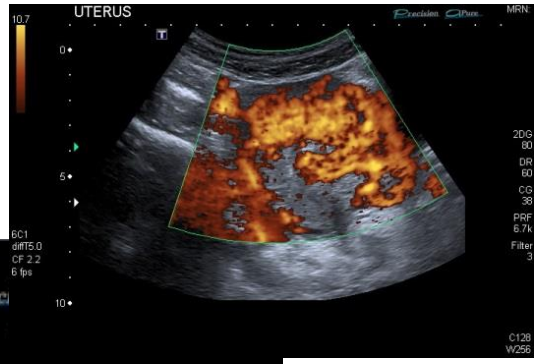
End of treatment





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Follow-up

- Continues regular hCG surveillance
- Advised to delay next pregnancy for 1 year after treatment
- Periods stopped during chemotherapy, restarted about 3-4 months after completion of treatment
- Visited fertility department before trying for a family
- AMH 0.07 pmol/L
- Three months later: viable conception

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Learning points

Indications for treatment

- **Plateaued or rising hCG**
- **Choriocarcinoma**
- **Mets in liver, brain, GI tract**
- **hCG > 20,000 IU/L 1 mnth post evac**
- **Lung mets > 2 cms**
- **Bleeding**
- **hCG elevated after 6 months**

Agarwal et al Lancet 2012

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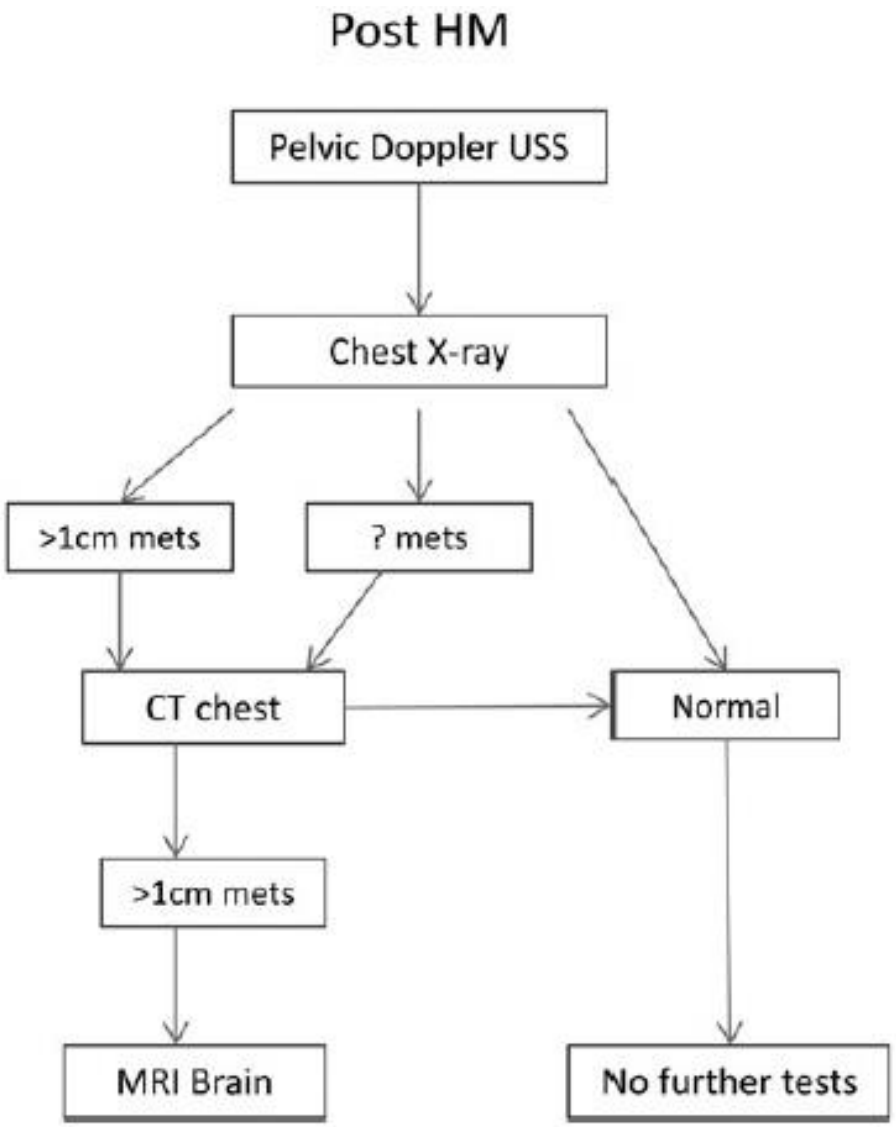
Investigations



Post other pregnancy or on relapse

- Pelvic Doppler USS
- MRI pelvis
- CT chest / abdo
- MRI brain
- */- CT-PET scan

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FIGO scoring system:
Risk of resistance to single agent therapy

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

Low Risk 0-6, High Risk >6

Kohorn et al Int J Gynecol Cancer 2000

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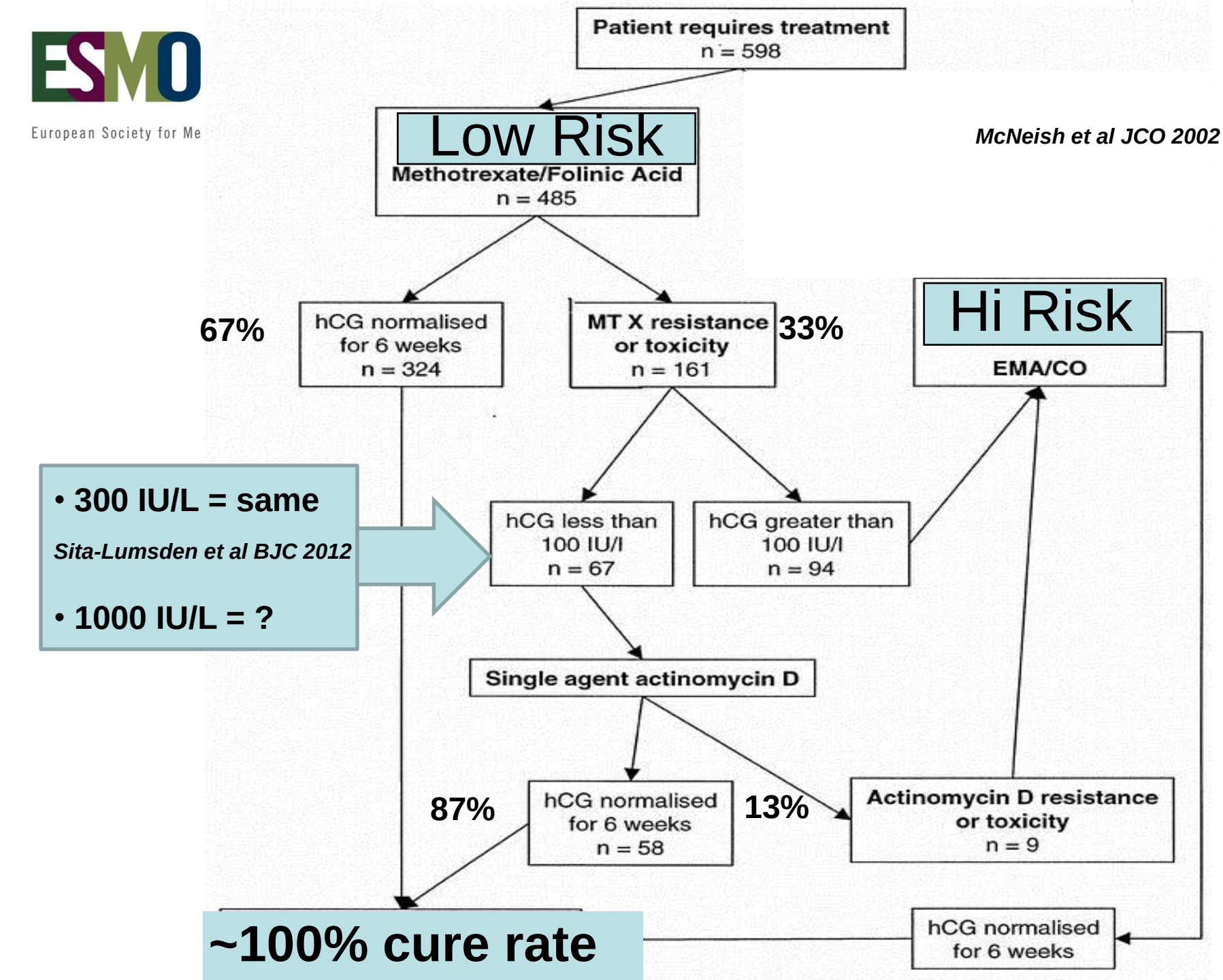
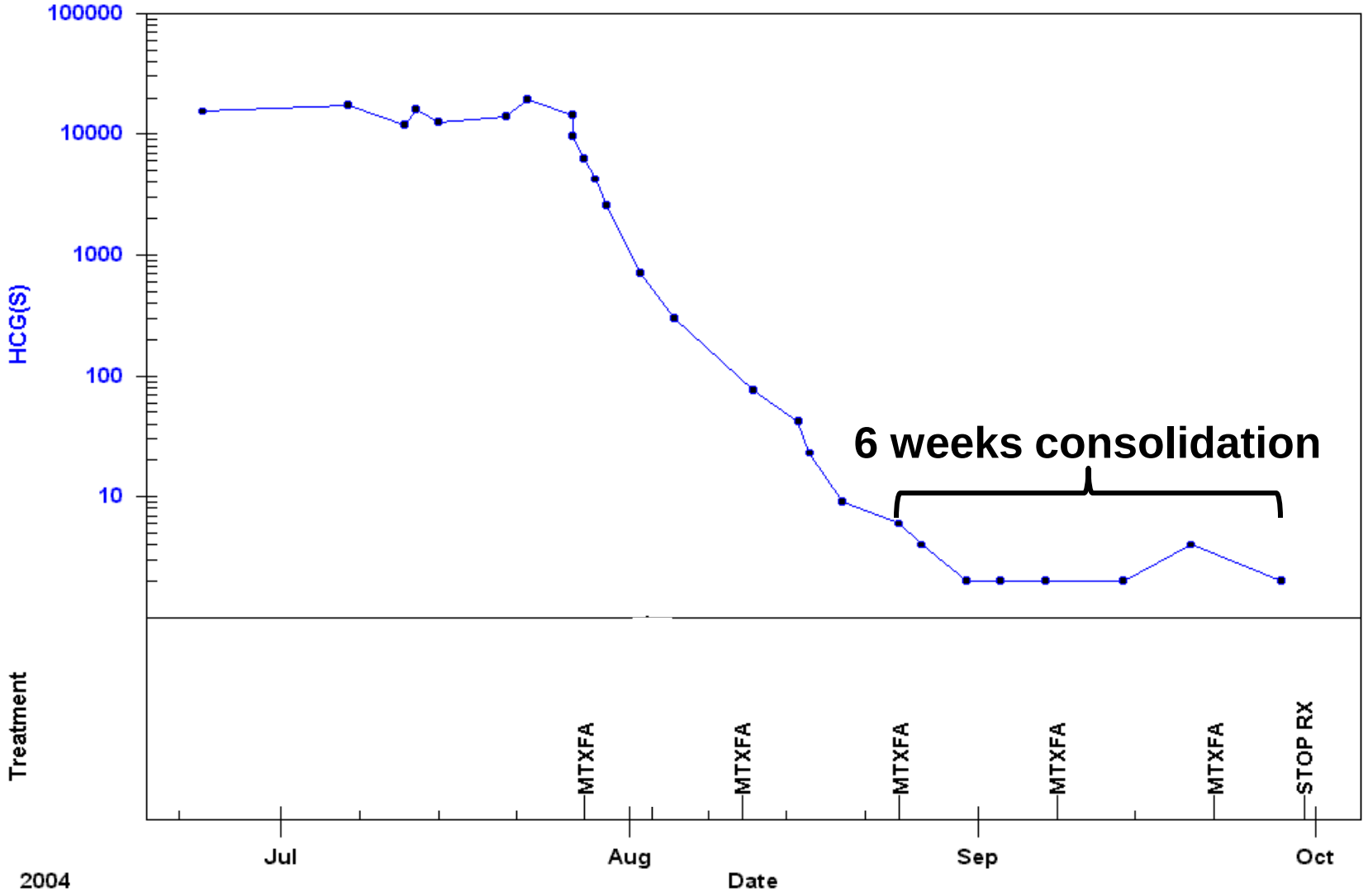

Patient requires treatment
n = 598
Low Risk
Methotrexate/Folinic Acid
n = 485
McNeish et al JCO 2002
67%
hCG normalised
for 6 weeks
n = 324
MT X resistance
or toxicity
n = 161
33%
Hi Risk
EMA/CO
• 300 IU/L = same
Sita-Lumsden et al BJC 2012
• 1000 IU/L = ?
hCG less than
100 IU/l
n = 67
hCG greater than
100 IU/l
n = 94
Single agent actinomycin D
87%
hCG normalised
for 6 weeks
n = 58
13%
Actinomycin D resistance
or toxicity
n = 9
hCG normalised
for 6 weeks
~100% cure rate

Duration of Consolidation therapy



4 weeks = relapse rate doubles

Hi risk poor prog = 8 weeks consolidation

Lybol et al Gynecol Oncol 2012

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High Risk Treatment

EMA	
Day 1	Dactinomycin 0.5 mg IV bolus
	Etoposide 100 mg/m^2 over 30 minutes
	Methotrexate 300 mg/m^2 over 12 hours
Day 2	Dactinomycin 0.5 mg IV bolus
	Etoposide 100 mg/m^2 over 30 minutes
	Folinic acid 15 mg PO bid for 2 days commencing 24 hours after start of methotrexate
CO	Vincristine 0.8 mg/m^2 (maximum 2 mg) bolus
	Cyclophosphamide 600 mg/m^2 over 30 minutes
	EMA and CO alternate weekly

Bower et al JCO 1997, Alifrangis et al JCO 2013

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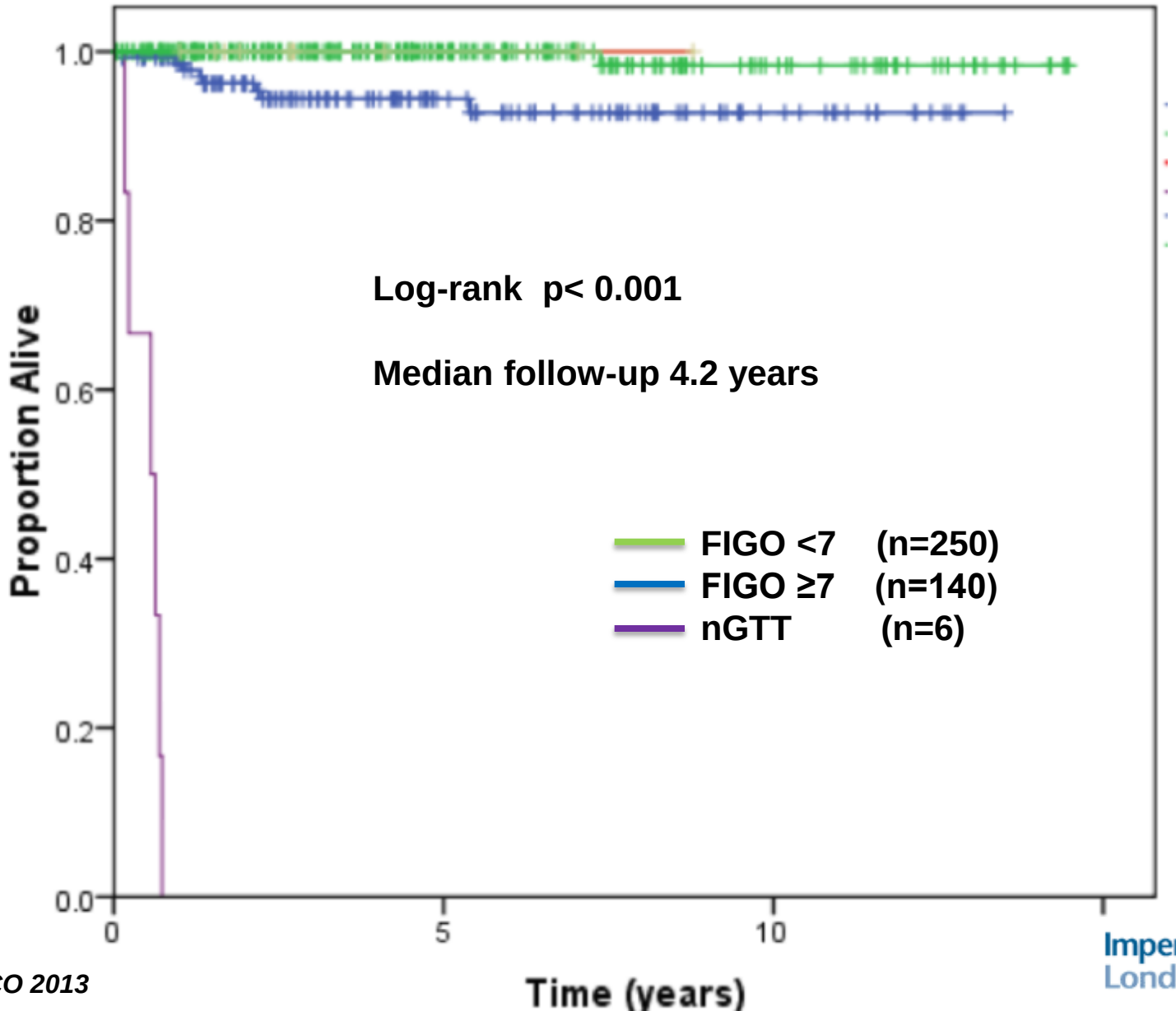
1995-2010 EMA/CO survival data



Alifrangis et al JCO 2013

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Long-term outlook

Chemotherapy

↓

Remission ← **3% relapse**

↓

Life long hCG follow-up

↓

83% successful pregnancies

- **AMH test value ?? nonsense**

EMA/CO - **hastens menapause ~ 3 yr**
- **no increased risk 2nd tumours**

Early pregnancy - **no increase in abnormal fetus**
- **no increase in relapse rate**

Rustin et al JCO 1996
Woolas et al BJOG 1998
Blagden et al BJC 2002
Savage et al JCO in press

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Acknowledgements

Dr Naveed Sarwar

Prof Neil Sebire

Dr Baljeet Kaur

Dr Rosemary Fisher

Dee Short

Sabrina Positano

Karina Catalano

Emma

Dr Anna Tommasi

Dr Roshan Agarwal

Dr Philip Savage

Prof Edward Newlands

Prof Ken Bagshawe

Mr Richard Smith

Mr Angus McIndoe

Miss Christina Fotopolou

Carol Sammut

Roxanne Nyei

Dr Adam Mitchell

Dr Adrian Lim

Daksha Patel

Hugh Mitchell

Dr Richard Harvey

Sarah Strickland

Linda Dayal

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wellcome trust

NCRN National Cancer Research Network

CTRI

MRC Medical Research Council

DH Department of Health

CANCER RESEARCH UK

ECMC

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