

# Less is not always more: Systemic treatment and surgery of relapsed and refractory testis cancer

## Patient cases

## Treatment of high risk testis cancer

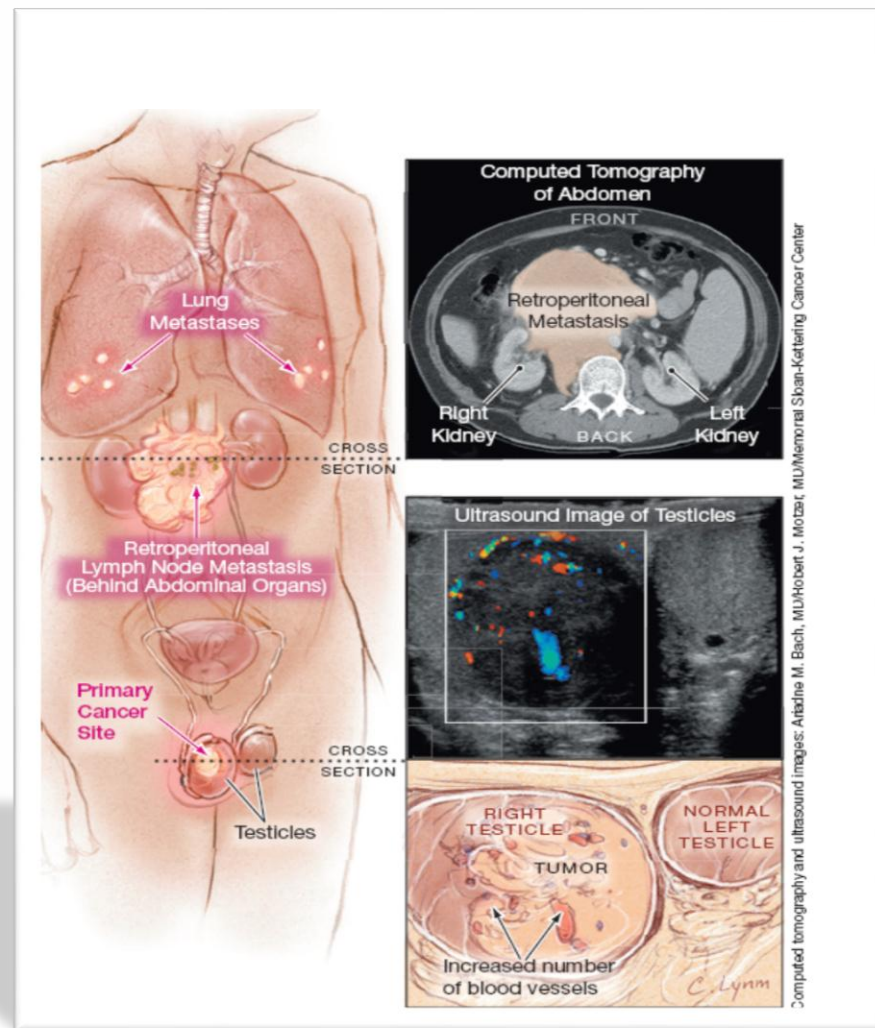
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# Testicular germ cell tumors

	NSGCT	SGCT
Stage I	60%	80%
Stage II	20%	15%
Stage III	20%	5%



# IGCCCG risk stratification model

Prognosis	5-year survival	Seminoma	Non-seminoma
Good	90%	<ul style="list-style-type: none"> <li>Any primary location</li> <li>No non-pulmonary visceral metastases</li> <li>Any marker level</li> </ul>	<ul style="list-style-type: none"> <li>Testis or primary extragonadal retroperitoneal tumor</li> <li>No non-pulmonary visceral metastases</li> <li>Low markers</li> <li>AFP &lt; 1,000 ng/ml</li> <li>HCG &lt; 5,000 IU/l</li> <li>LDH &lt; 1.5 x normal level</li> </ul>
Intermediate	75%	<ul style="list-style-type: none"> <li>Any primary location</li> <li>Presence of non-pulmonary visceral metastases (liver, CNS, bone, intestinum)</li> <li>Any marker level</li> </ul>	<ul style="list-style-type: none"> <li>Testis or primary extragonadal retroperitoneal tumor</li> <li>No presence of non-pulmonary visceral metastases</li> <li>Intermediate markers</li> <li>AFP 1,000-10,000 ng/ml</li> <li>HCG 5,000-50,000 IU/l</li> <li>LDH 1.5-10 x normal level</li> </ul>
Poor	50%	<ul style="list-style-type: none"> <li>Does not exist</li> </ul>	<ul style="list-style-type: none"> <li>Primary mediastinal GCT with or without testis</li> <li>Primary retroperitoneal tumor</li> <li>Presence of non-pulmonary visceral metastases (liver, CNS, bone intestinum)</li> <li>High markers</li> <li>AFP &gt; 10,000 ng/ml</li> <li>HCG &gt; 50,000 IU/l</li> <li>LDH &gt; 10 x normal level</li> </ul>

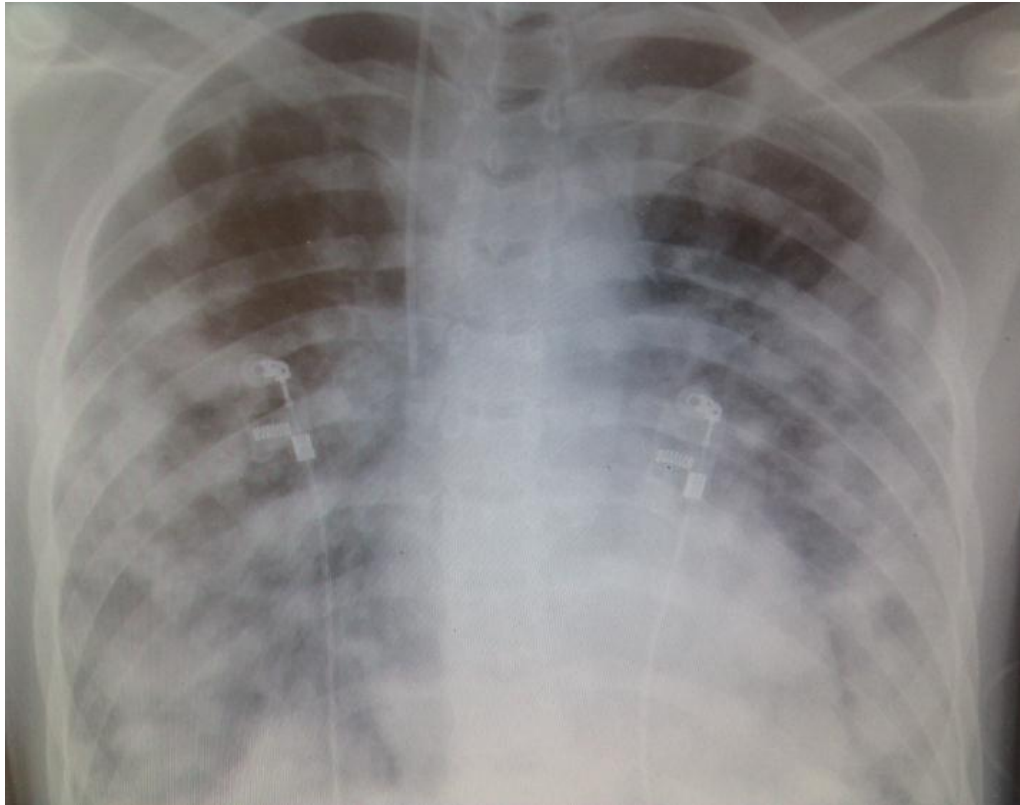
[International Germ Cell Cancer Collaborative Group, JCO 1997]

# Case I

- 17 year old young man
- **Severe dyspnea**
- Weight loss
- Fatigue
- Intermittent fever
- Abdominal pain
- Polyuria & Polydipsia

# Case I - Diagnostics

## Case I: Chest X-ray



- Multiple, bipulmonary nodules mainly in both inferior lobes plus right middle lobe, partially confluent

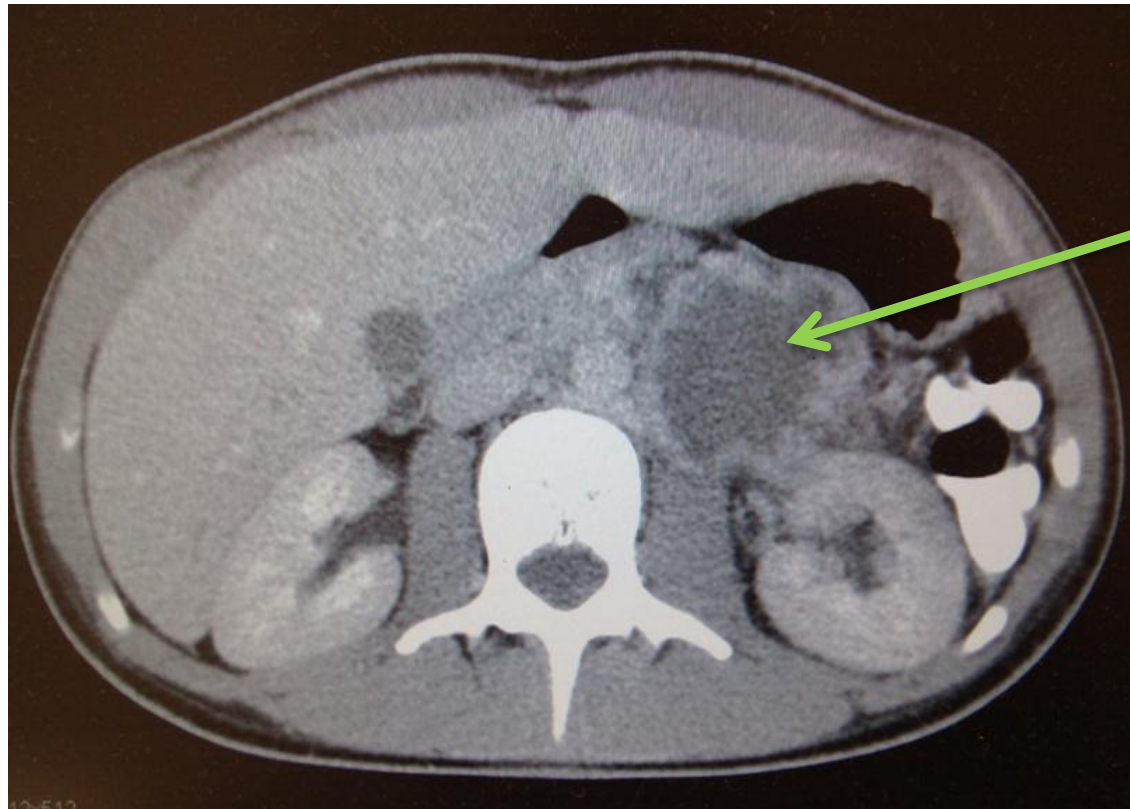
# Case I: CT-scan of the chest



- Multiple intrapulmonary masses, defined by an extensive metastatic invasion.



# Case I: CT scan of the abdomen

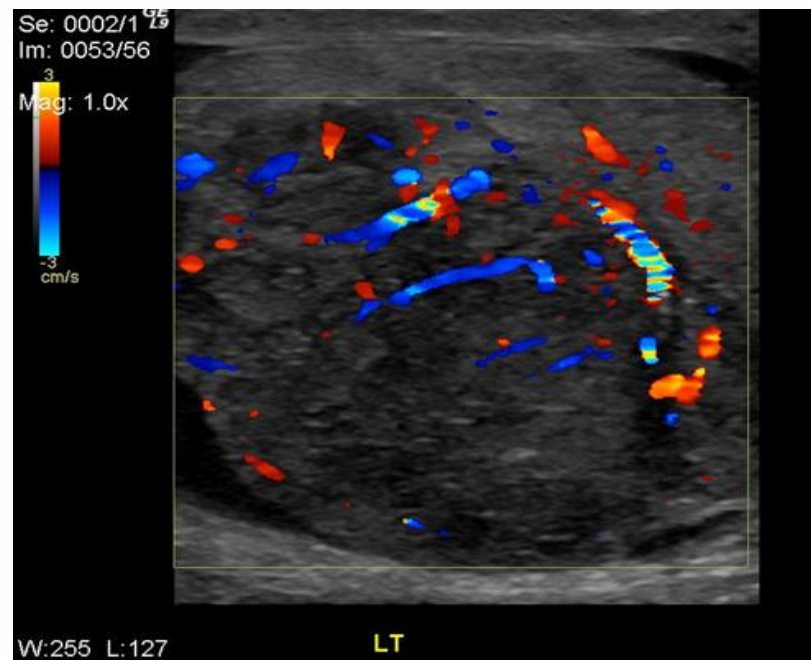


- 5.3 x 4.8 cm lymphonodal mass close to the pancreatic tail



# Case I: Ultrasound of the testes

- Left testis with a testicular mass (1.5 x 1.3 cm) showing an inhomogeneous, highly vascularized tumor



# Serum tumor markers and other lab values at initial diagnosis

- beta-hCG  $2.39 \times 10^6$  U/l [ $< 3$  U/l]
- AFP 21.3 kU/l [ $< 5$  kU/l]
- LDH 835 U/l [ $< 250$  U/l]
- TSH  $< 0.005$  mU/l [0.27-4.2 mU/l]
- fT4  $> 7.77$  ng/dl +++

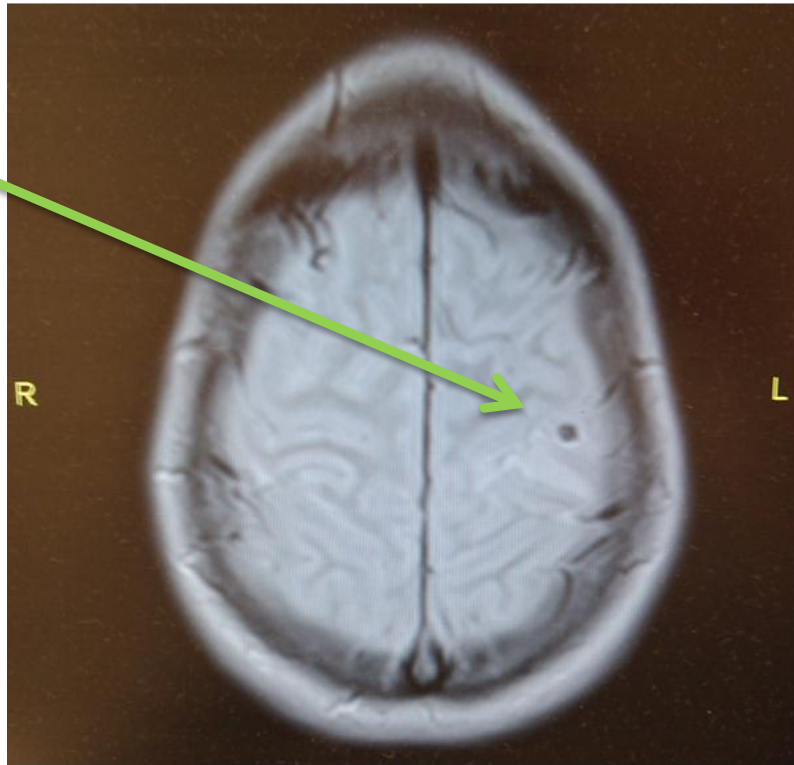
- Most likely diagnosis of metastatic NSGCT
- Thyroid disease ????

# Serum tumor markers and other lab values at initial diagnosis

- beta-hCG  $2.39 \times 10^6$  U/l [ $< 3$  U/l]
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- fT4  $> 7.77$  ng/dl +++

- Most likely diagnosis of metastatic NSGCT
- **(beta-hCG induced) hyperthyreodism**

# Case I: MRI of the neurocranium



- Metastases in the left hemisphere with perifocal edema, in the right splenium and in the pinealis area
- Central nervous diabetes insipidus (due to pinealis metastasis)

# Case I: Findings at initial diagnosis (04/2011)

**Entity:** Nonseminomatous germ cell tumor (NSGCT)

**Histology:** Primarily unknown

**Primary site:** Left testicle

**Staging:** pTx N3 M1b (brain) S3

**AJCC/UICC:** Stage IIIC

**IGCCCG:** Poor risk

**Complications:** Pulmonary insufficiency,  
diabetes insipidus, betaHCG-induced thyreotoxicosis

## ➤ Do we need further diagnostics

- **Histology (via orchiectomy) ?**
- **PET scan ?**
- **Bone scan ?**

➤ Due to poor clinical condition and poor risk life-threatening disease orchiectomy was not performed before start of chemotherapy.

[Ondrus et al., Int J Androl 2001]

## ➤ What would be your treatment recommendation?

- **Chemotherapy alone?**
- **Add whole brain radiotherapy?**
- **Include surgery of brain mets?**



# Suggestions for systemic therapy

**(1) 4 x BEP**

**(2) 4 x VIP**

**(3) Primary high-dose CTx (e.g., 3 x HD-VIP) after induction CTx (1 x VIP) with autologous stem cell harvest**

**(4) Methotrexate based first-line regimen (e.g., POMB-ACE)**

**(5) Single agent caboplatin due to poor performance status**

# EGCCCG guidelines

Approximately 10% of all patients with advanced germ cell cancer present with brain metastases (ie, 1–2% of all patients with testicular cancer).

The optimal sequence of treatment modalities (chemotherapy, radiotherapy, surgery) has not yet been finally defined.

In a multivariate analysis cranial irradiation added to systemic chemotherapy improved the overall prognosis of patients who present with brain metastasis [EBM III: 70], which contrasts with earlier reports demonstrating no benefit from additional cranial irradiation.

It has not yet been defined whether postchemotherapy irradiation of the CNS is required after complete remission has been achieved by chemotherapy alone.

There is no evidence that high-dose chemotherapy plus autologous haematopoietic stem cell support given as part of first-line therapy increases survival.

[Krege et al., Eur Urol 2008]

# Therapy in metastatic GCT

Risk group	5 YS	Therapy	EBM-level
“good prognosis”	90 %	3 x PEB	( I B)
seminoma / non-seminoma		[*alternativly 4 x PE]	( II A)
“intermediate prognosis”	80 %	4 x PEB	( IV)
seminoma / non-seminoma		[*alternativly 4 x PEI]	( I B)
“poor prognosis”	50 %	4 x PEB	( I B)
non-seminoma		[*alternativly 4 x PEI]	( I B)
* If contraindication to use of bleomycin			

No primary but secondary use of prophylactic G-CSF  
(e.g. after neutropenic fever episode)

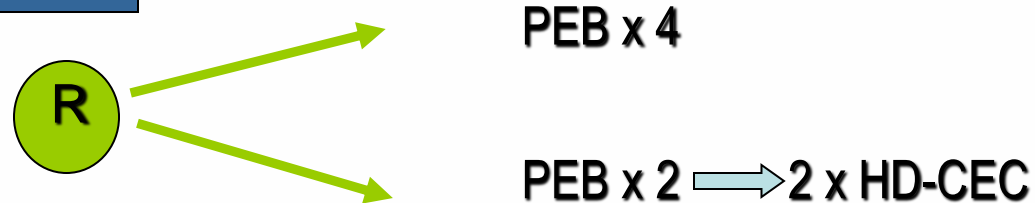
European Germ Cell Cancer Consensus Group 2011

# Case I: Initial chemotherapy

- 1 cycle of **Cisplatin 20mg/m<sup>2</sup> + Etoposide 75mg/m<sup>2</sup> (PE)**  
(days 1-3 only, due to poor clinical condition)
  - Respiratory failure due to wide spread metastases
  - Required ventilation
  - Complications: Pneumothorax + pulmonary bleeding
- At recovery (day 14)  
1 cycle **Cisplatin 20mg/m<sup>2</sup> + Etoposide 75mg/m<sup>2</sup> + Ifosfamide 1200mg/m<sup>2</sup> (VIP) (day 1-5)**
  - Subsequent autologous stem cell harvest (3 x 6.3x10<sup>6</sup> CD34+ cells)

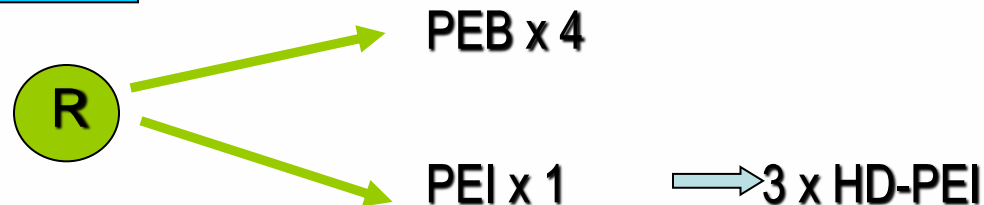
# Primary HD-Ctx in “high risk” GCT

## US - Intergroup



- “intermediate and poor prognosis”
- started 1996, published 2008, 220 pts

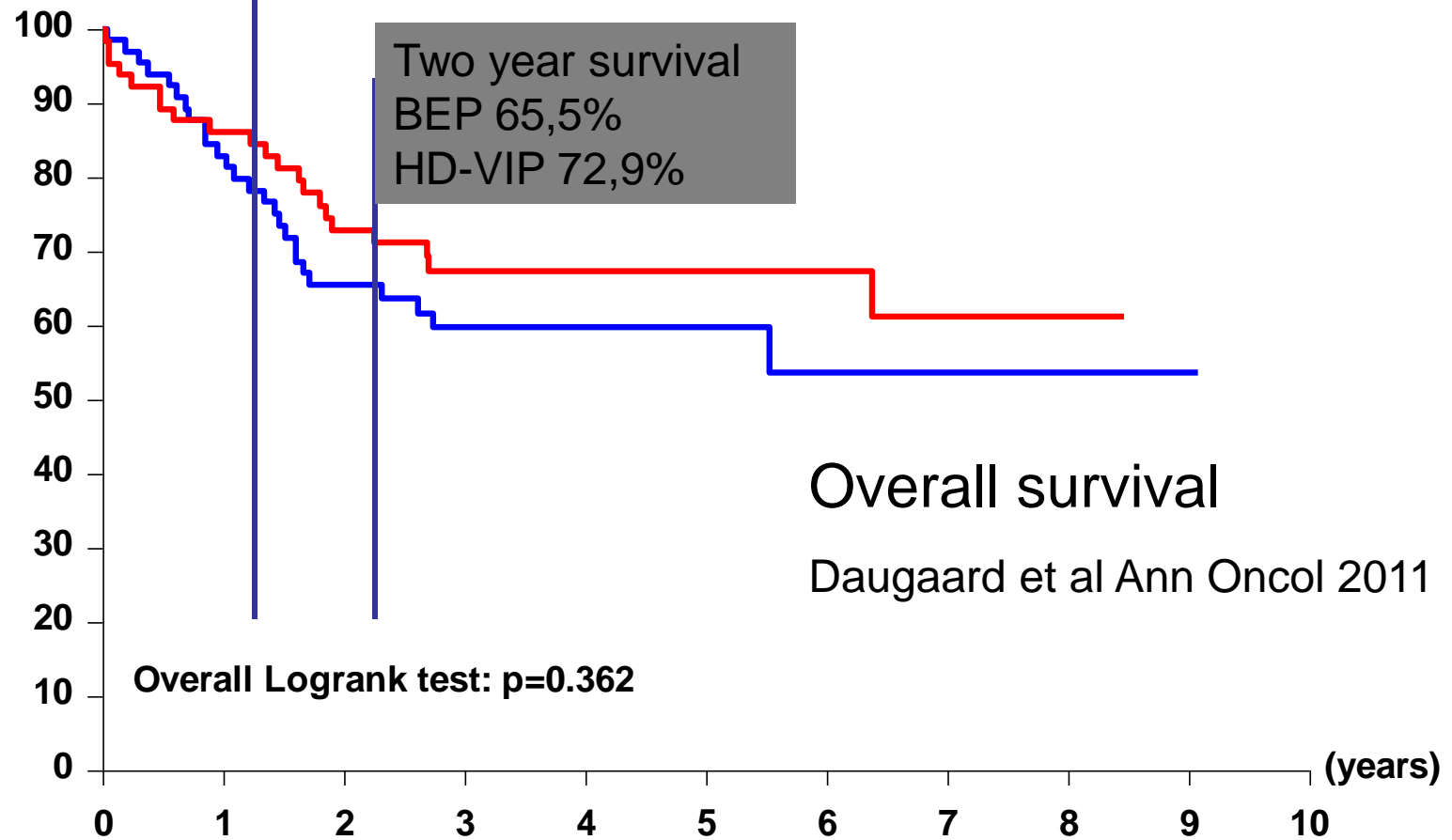
## EORTC



- “poor prognosis”
- started 1999, 140/240 pts recruited. Published 2011

One year survival  
BEP 83%  
HD-VIP 86,1%

Two year survival  
BEP 65,5%  
HD-VIP 72,9%



O	N	Number of patients at risk :										Treatmen
26	66	53	39	29	22	14	9	5	2	1	—	BEP
21	65	53	42	32	24	15	11	6	2	0	—	HD-VIP

# Conclusion first line high-dose CTX

- Data for high-dose therapy only in poor-risk pts
- Feasible with acceptable toxicity
- In randomised studies no statistically significant difference compared to 4 cycles of standard PEB
- (better ?) regimen: sequential intermediate HD CTX (HD-PEI)
- Subgroups, which profit may profit most likely:
  - Pts with inadequate marker decline during first 1-2 cycles of PEB
  - very poor risk pts:  
primary mediastinal GCT, CNS mets, (liver mets ?)  
(Phase II in CNS mets 24pts, 75 % OS

Kollmannsberger Ann Oncol 2002)

→ Current approach in Germany: national treatment registry accepted after discussion with insurance companies



# Case I: Further treatment

- **05-07/2011: 3 cycles high-dose CTx (HD-VIP)**

**Cisplatin 20mg/m<sup>2</sup> + Etoposide 300mg/m<sup>2</sup> + Ifosfamide**

**2000mg/m<sup>2</sup> (days 1-5 of each cycle) with autologous PBSCT  
(day 7 of each cycle)**

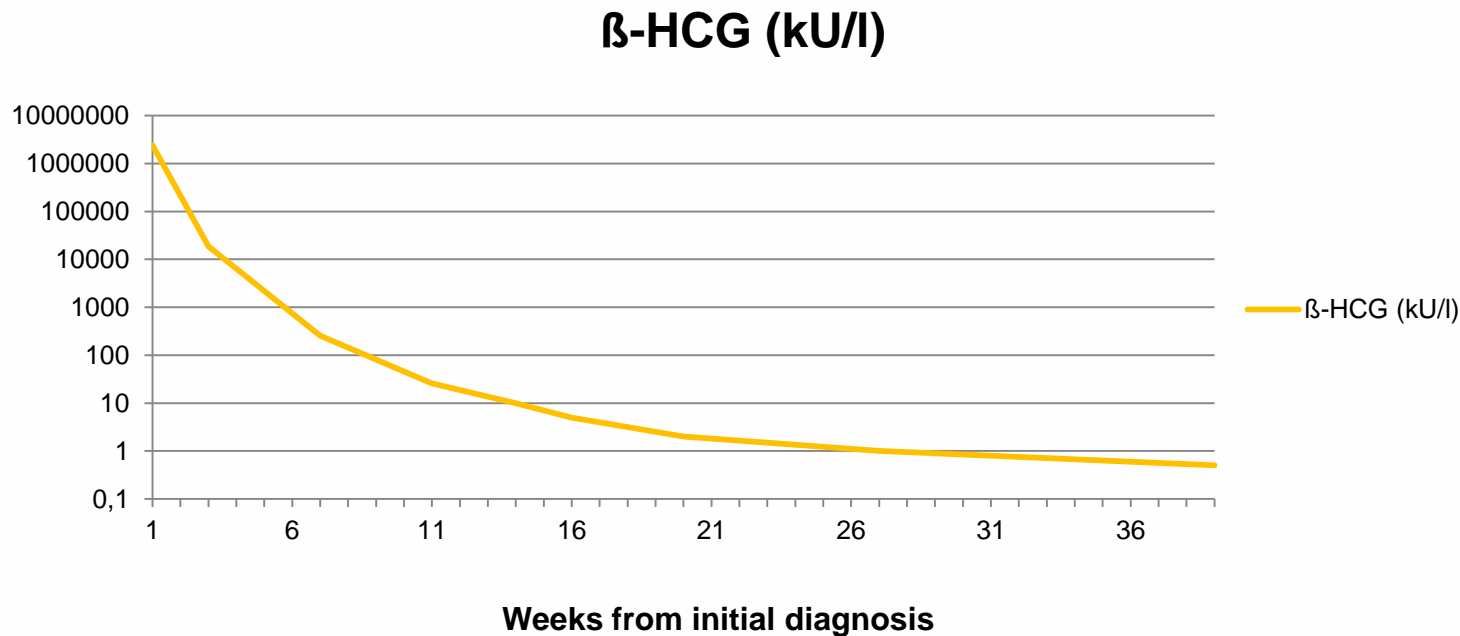
- **Complications: Febrile neutropenia after 1<sup>st</sup> cycle**
- **Result : PR M -**

- **09/2011: RPLND + Ablatio of left testis (→necrosis)**

- **Resection of multiple pulmonary residues not feasible**

- **10/2011: WBR (30 Gy in total, 10 x 3 Gy fractions)**

# Case I: Treatment response

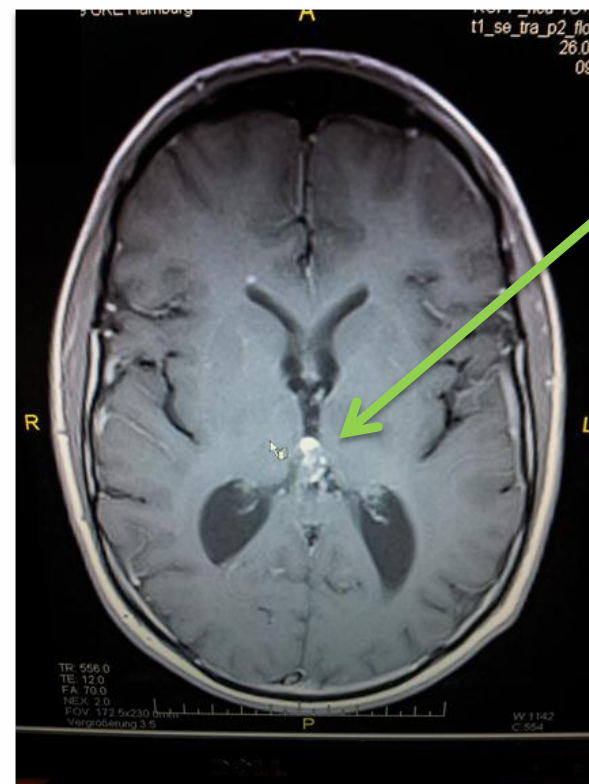
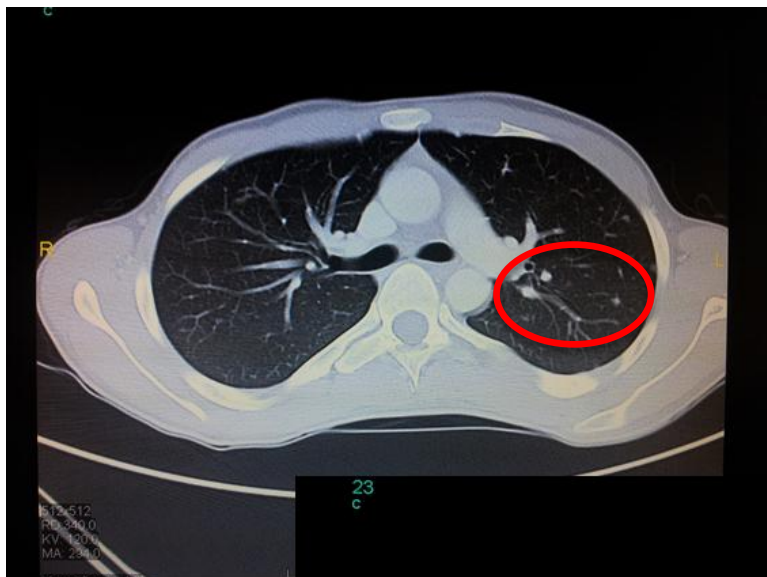


- After systemic treatment remission with normalization of TM after 3rd cycle of HD-CTX (adequate decrease ( $t_{1/2}=7d$ ))
- Normalization of diuresis during CTX and by Desmopressin

# Case I: Further treatment

- **09/2011: RPLND + Ablatio of left testis**  
**(histology: →necrosis)**
  - **Resection of multiple pulmonary residues not feasible**
- **10/2011: WBR (30 Gy in total, 10 x 3 Gy fractions)**  
**why? : due to residuals on MRI**

# Case I: Re-staging after CTx and FU



# Beta hCG & Thyreotoxicosis

- Excess hCG secretion, analogous to hyperemesis gravidarum and/or hydatidiform mole  
[Tilbrook et al., Ann Clin Biochem 2004]
    - Severity of emesis correlating with hCG level
  - Structural homology in both TSH and hCG molecules as well as TSH and hCG receptors  
[Yoshimura & Hershman, Thyroid 1995]
  - Approximately 50% of patients with beta-hCG >50.000 U/l have hyperthyroidism
  - Symptoms may overlap with those of extensive metastatic disease  
[Oosting et al., Ann Oncol 2010]
- 
- Case I: Antithyroidal therapy with carbimazole & propranolol
    - Fast normalization of thyroid function after initial chemotherapy
    - Rehabilitation of thyroid function equal to drop of beta-hCG during CTX

# Neuroendocrine aspects of pineal tumors

- GCTs of CNS constitute 3 % of primary pediatric brain tumors
- Primary CNS-GCTs are most commonly located in the pineal and suprasellar regions of the brain [Echevarria et al., Oncologist 2008]
- Clinical symptoms vary by location and size
  - Endocrine abnormalities, visual changes, increased intracranial pressure [Echevarria et al., Oncologist 2008]
- Only boys develop precocious puberty with pineal tumors
  - Actually pseudoprecocious puberty, due to ectopic hCG production
- Diabetes insipidus with pineal tumors is usually due to spread to the hypothalamus by ventricular seeding

[Fetell & Stein, Neurol Clin 1986]

# Case I:

## Follow up at one year after therapy (9/2012)

- PR in lungs (lesions slowly regressing)
- Tumor markers negative
- No thyroid abnormalities, no medication
- No diabetes, no medication
- Fully active young man  
having just completed high school

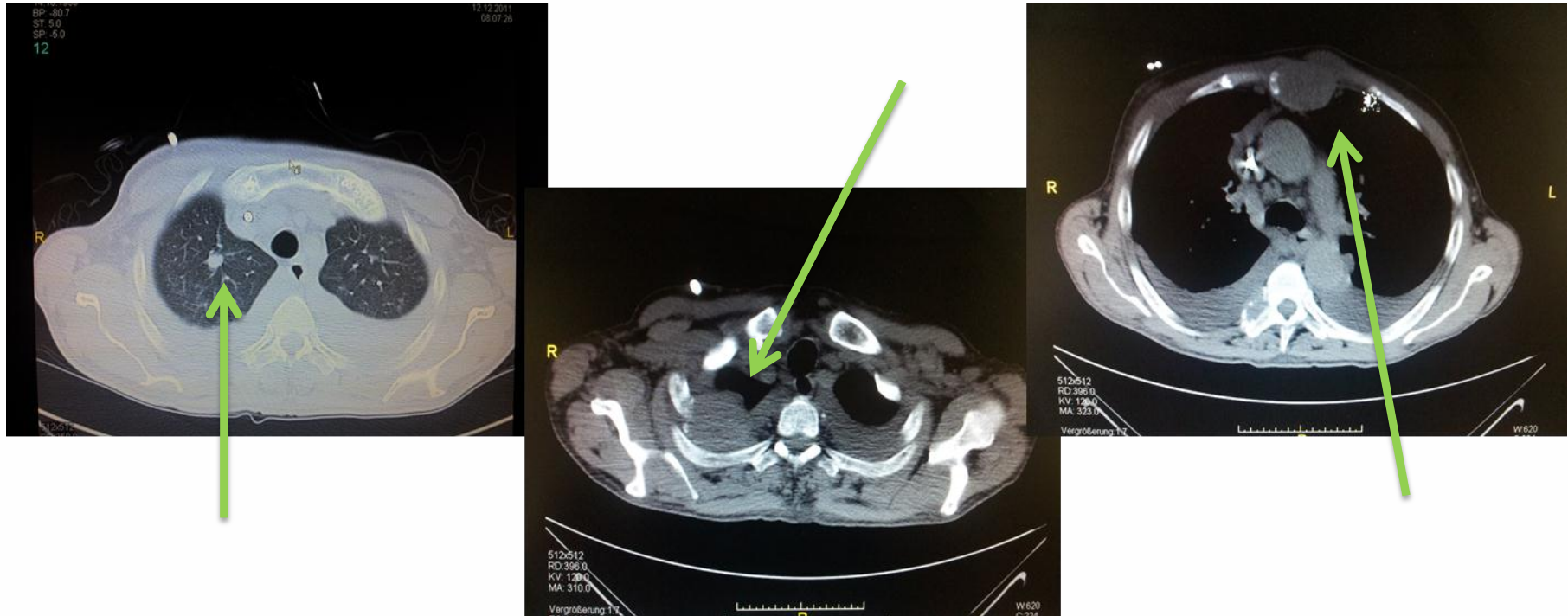


# Case II

- 58 year old male
- Weight loss
- Back pain
- Massive swelling of left testicle (17x22.5 cm, 3.800g)
- Arterial hypertension
- Wegener's granulomatous disease with terminal renal failure
- Daily peritoneal dialysis, diuresis ~20-50ml/day
- Hyperparathyroidism

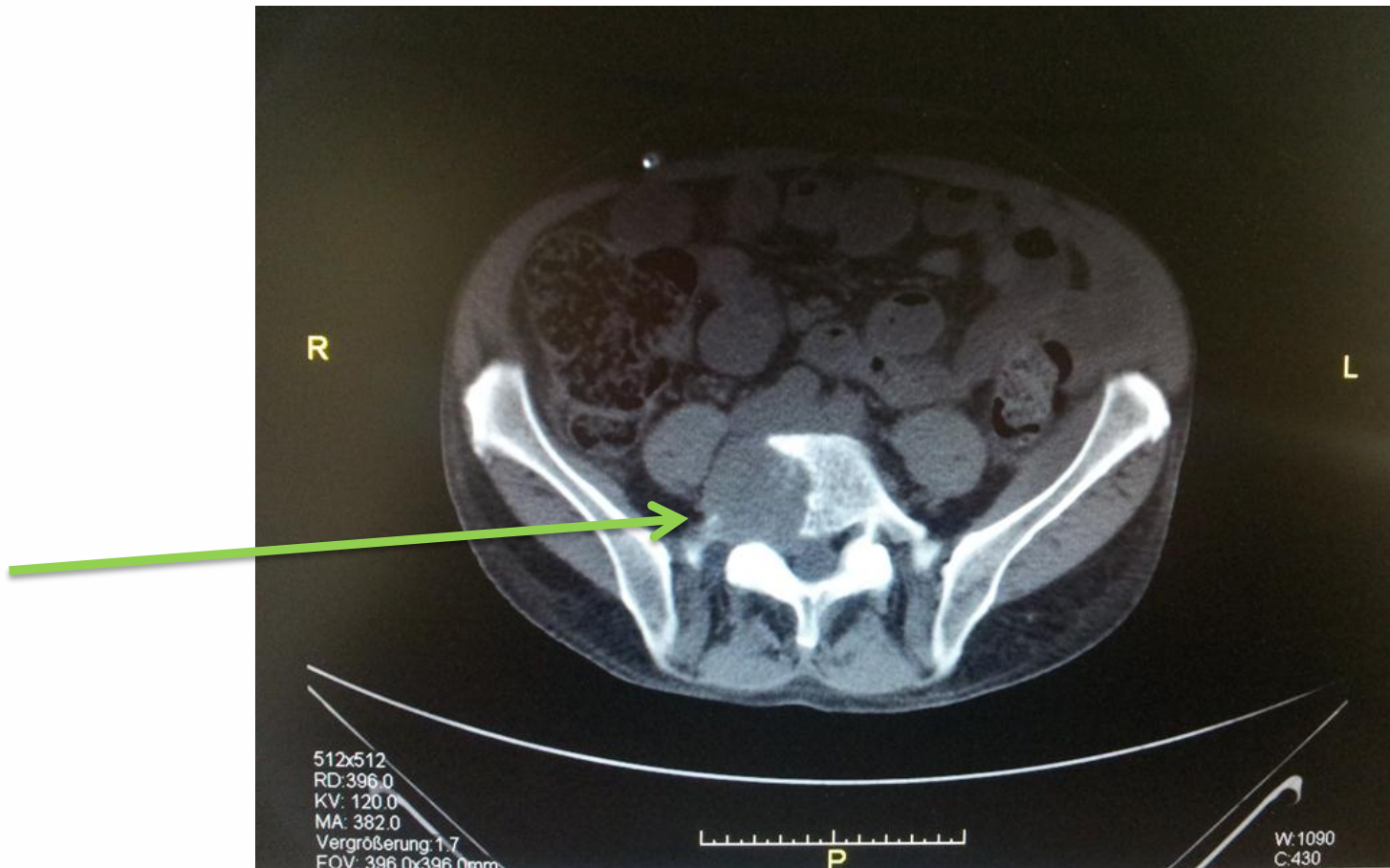
# Case II - Diagnostics

## Case II: CT scan of the thorax



- Pulmonary metastases, Costa dextra II, pathologic fracture Costa sinistra VIII

## Case II: CT scan of the abdomen



- Metastatic lesions found in os ileum bilaterally, lumbar vertebra 5

# Case II: Further radiographic imaging

- Bone scan (scintigraphy)
  - Low intensity signal in sternal metastasis
  - No signal of known metastases in costa dex II, costa dex VI, left os ileum, sacral vertebra 1
  - High intensity signal right acetabulum, right maxilla, right calcaneus, both lower legs
  
- CT scan of the brain
  - Distinct cerebrosclerosis, decreased brain volume
  - No intracerebral metastases detectable

# Serum tumor markers and clinical symptoms at initial diagnosis

- $\beta$ -HCG      101.614 U/l      [ $< 3$  U/l]
- AFP      115 kU/l      [ $< 5$  kU/l]
- LDH      486 U/l      [ $< 250$  U/l]
- Inguinal orchiectomy of large right testicle
- Bilateral paresis of foot extensors
  - Spine-surgery: Dorsal spondylodesis + debulking L4-S1 12/2011
- Switch from peritoneal dialysis to intermittent hemodialysis

## Staging at initial diagnosis (12/2011)

**Entity:** Nonseminomatous germ cell tumor (NSGCT)

**Histology:** EC, Yolk sac tumor, Chorioncarcinoma,  
immature teratoma

**Primary site:** Right testicle

**Staging:** pT4 Nx M1b L0 V1 (bone/pleural/pulmonary)

**AJCC/UICC:** Stage IIIc

**IGCCCG:** Poor risk (markers, bone)

**Comorbidity:** Renal failure with dialysis therapy, Wegeners disease, arterial hypertension, hyperparathyroidism



# What would be your treatment recommendation?

# Suggestions

- (1) 4 x BEP**
- (2) 4 x VIP**
- (3) 4 x Cisplatin/Etoposide**
- (4) 4 x BEP or VIP or PE but with Carboplatin instead of Cisplatin**
- (5) None of the above mentioned, because platinum-based chemotherapy is not feasible in patients with renal impairment**

## Case II: Initial chemotherapeutic treatment

- **12/2011: 1st. cycle Carboplatin AUC4 d1 (1h) (GFR 0 ml/min, 100mg) + Etoposide 75mg/qm d1-3 (1h) + Ifosfamide 1.200mg/qm d1+2 (2h)**
  - Complications: Ifosfamide-induced neurotoxicity (CNS), hypertensive urgency, pleural effusion
  - Daily hemodialysis prior to next chemo infusion (d1-6)
  - No cisplatin used due to neutotoxicity and poor audiogram
  - → how to proceed?

## Case II: Further chemotherapy

- **01/2012: #2 Carboplatin AUC4 d1 (GFR 0ml/min = 100mg) + Etoposide 75mg/qm d1-5**
  - AIM: Reduce toxicity
- **02-04/2012: #3-5 Carboplatin AUC5 (GFR 0ml/min = 125mg) + Etoposide 75mg/qm d1-5 + Paclitaxel 135mg/qm d2 (3h)**
  - AIM: Increase efficacy by 3rd agent
  - AIM: 5th cycle to compensate for potential underdosing during first 2 cycles

# Chemotherapy in hemodialysis patients

- Data remain sparse for most cytotoxic drugs
- Careful adaptations to optimize drug exposure, ensure efficacy and reduce risk of side-effects
- Clearance by dialysis must be taken into account for appropriate chemotherapy timing

[Janus et al., Ann Oncol 2010]

- For most cytotoxic drugs no established guidelines on how to deal with overdosage available
- Only few data available about drug dialysability

[Tomita et al., Clin Pharmacokinet 2004]




# Dialysability of anticancer drugs

➤ 20 common anticancer drugs tested *in vitro*

Good	Intermediate	Poor
MTX 5-FU Ara-C Melphalan <b>Cisplatin</b> <b>Ifosfamide</b> Dactinomycin 4-OH-cyclophosphamide Dacarbazine	Doxorubicin Epirubicin Carmustine	Daunorubicin Vincristine Vinblastine <b>Etoposide</b> Mitoxantrone Teniposide

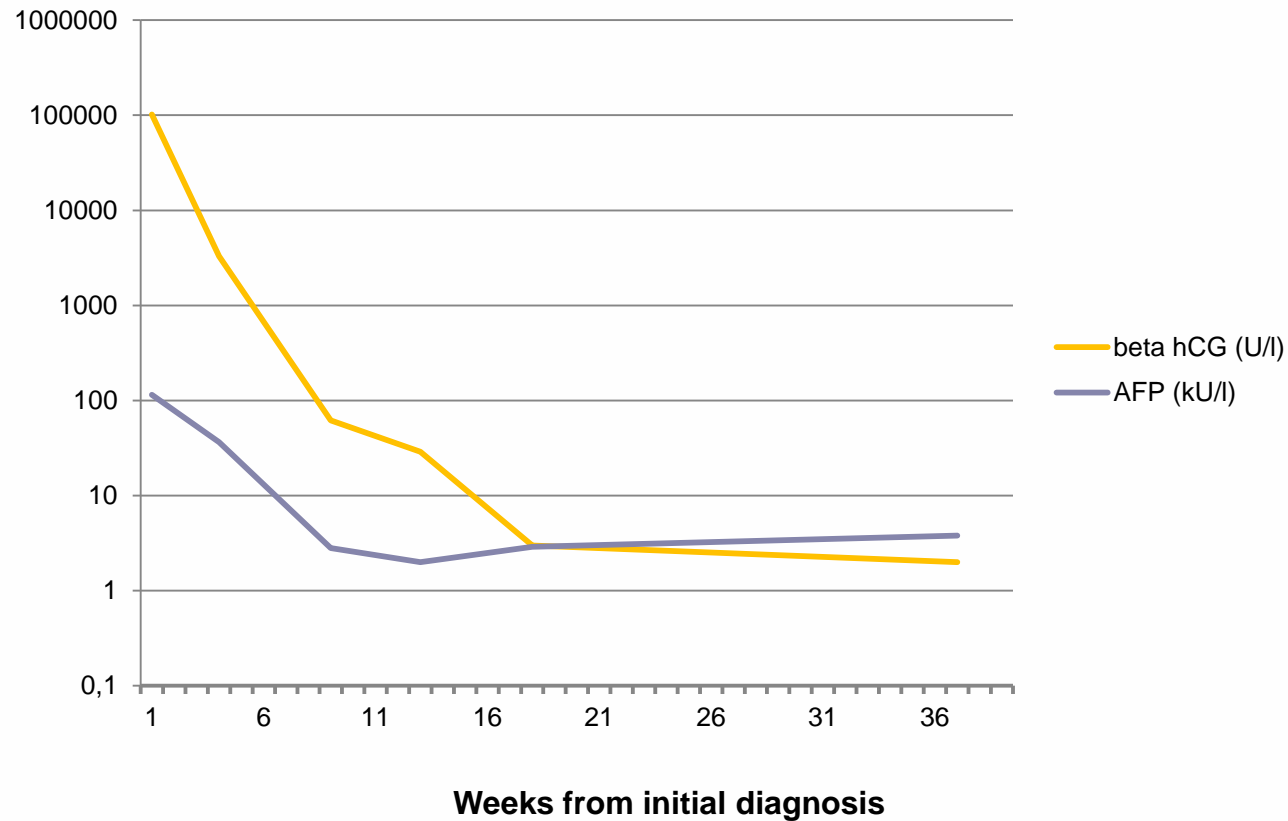
[Sauer et al., Cancer Treat Rev 2000 ]

# HD & Carboplatin, Etoposide, Paclitaxel

Carboplatin	Etoposide	Paclitaxel
<ul style="list-style-type: none"> <li><math>t_{1/2} = 5d</math> due to high plasma protein binding</li> <li>Risk of severe hematotoxicity at impaired renal function</li> <li>AUC increased by prolongation of time before HD</li> <li>Pharmacokinetics can be controlled by HD and interval between CTX and HD</li> <li>Delay of 16 hours between CTX and HD recommended</li> </ul>  <p><b>Dosage calculation should AUC-directed with GFR set equal to 0</b></p>	<ul style="list-style-type: none"> <li>Cytotoxicity dependend on concentration and duration of exposure</li> <li>Good correlation eto-plasma clearance <math>\leftrightarrow</math> creatinine clearance</li> <li>Pharmacokinetics cannot be controlled by HD (<math>t_{1/2}</math>, 95% plasma protein binding, distribution volume)</li> </ul>  <p><b>Dose reduction to ~60% recommended</b></p>	<ul style="list-style-type: none"> <li>Extensive hepatic metabolism (CYP450)</li> <li>&lt;10% renal clearance</li> <li>No alteration of pharmacokinetics or side-effects by HD</li> </ul>  <p><b>No dose adjustment necessary</b></p> <p>[Tomita et al., Clin Pharmacokinet 2004]</p>

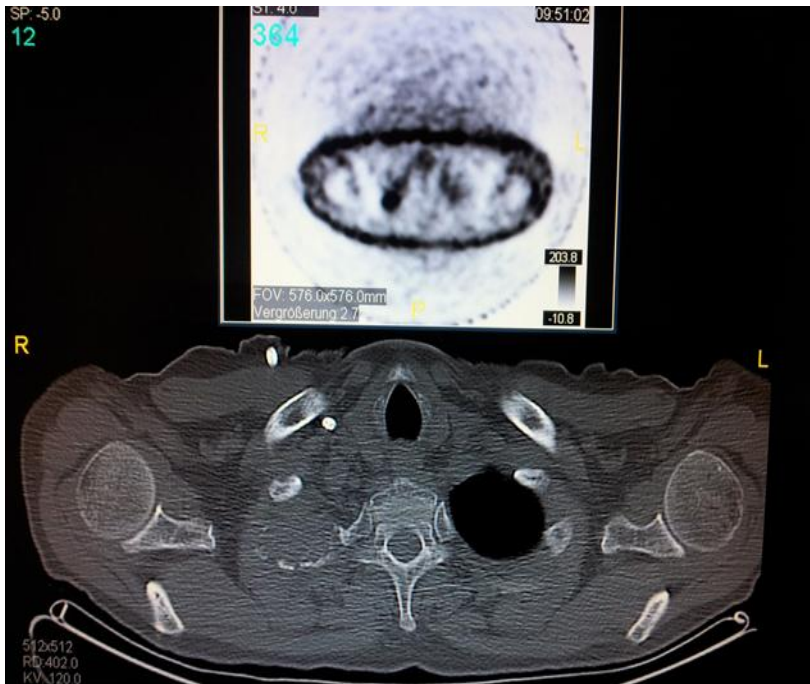
# Case II: Treatment response of TM

## Serum tumor markers





## Case II: Re-Staging by PET-CT after CTx



- 04/2012 PET-positive residuals at bone lesions, otherwise PET-negative
- No surgical/RTX options to resect all PET+ lesions (costa II dex, costa VI dex, sternum, LWK5, corpus ossis ilii dex, ala ossis ilii sin)

## Case II: FU 4 months CT scan



- 08/2012 no change of known bone lesions, no further metastases tumor markers negative
- Regular FU every 3 months to surgically resect potential recurrences

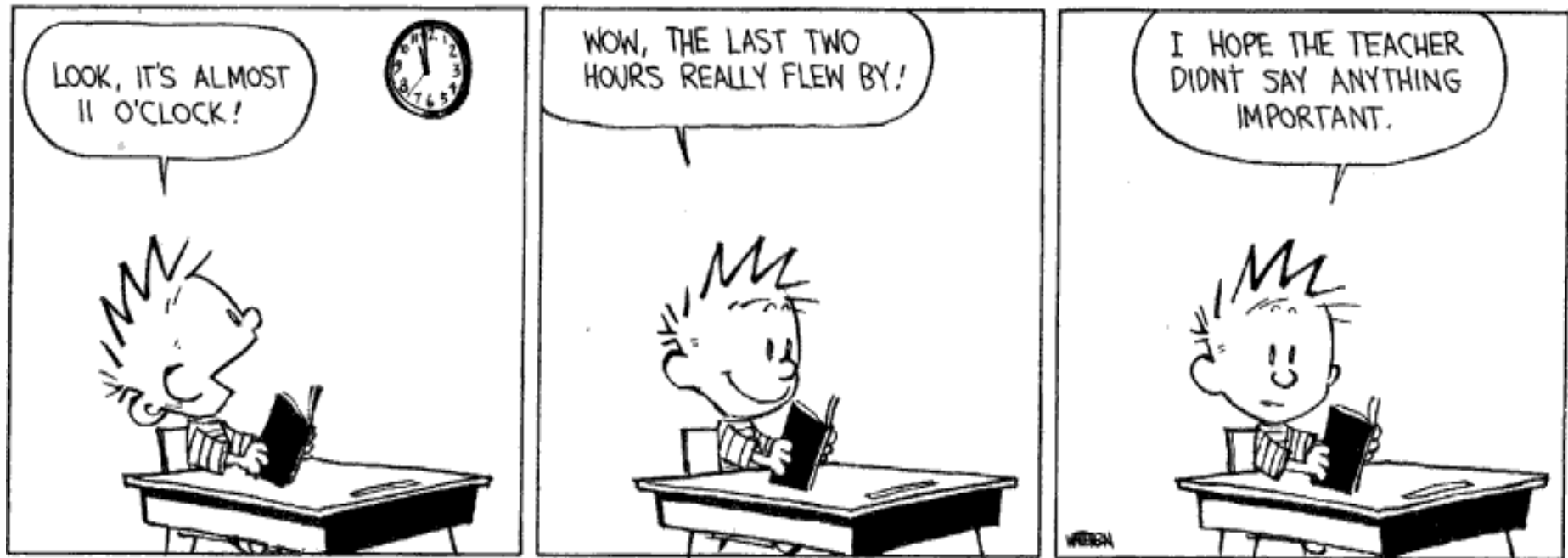
## ■ Case I

- Primary high-dose CTX may be beneficial in GCT pts with brain metastases
- Unusual complications of advanced disease (Diabetes insipidus, thyroreotoxicosis, pulmonary failure) [Oechsle et al., Eur J Cancer 2008 ]
- Patient progression free (M-) for 13 months since end of therapy

## ■ Case II

- Carbo/Eto/Tax (and Ifo) are potentially usable drugs in GCT pts undergoing hemodialysis
- Timing of HD after ctx important and individual dose adaption

# Thank you for your attention...



# Discussion

## Never give up on GCT patient