Treatment of Refractory and Late Relapse Testicular Cancer Patients

Christian Kollmannsberger MD FRCPC

Div. of Medical Oncology
BC Cancer Agency-Vancouver Cancer Centre
Dept. of Medicine, University of British Columbia

Associate Member
Dept. of Urologic Science, University of British Columbia

Vancouver, Canada

Disclosures:

No disclosures for this topic

Learning Objectives / Agenda

After reading and reviewing this material, the participant should be better able to understand:

- The clinical presentation of cisplatin-refractory disease
- Management options for cisplatin-refractory patients
- The presentation and biology of late recurrences
- The importance of a multi-disciplinary approach and the important role of surgery in the treatment of cisplatin-refractory disease and late recurrence

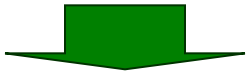
Cisplatin-refractory Disease and Late Relapse

Background

- Prognosis of relapse after second-line therapy is dismal
- Very small patient population
- Very few, small, non-randomized studies, including a heterogeneous patient population
  (early relapse, cisplatin-refractory, cisplatin-sensitive, late relapse....)
- No randomized studies to guide treatment decisions

Complexity of refractory and late relapse GCT patients

Decision making in the very rare patients with refractory GCT or late relapse is complex from deciding whether they have truly refractory disease or late relapse to therapeutic decisions regarding prognosis, the choice of the optimal treatment, timing and use of chemotherapy, incorporation of expert surgery and post chemotherapy management.



These patients can most benefit from being presented to an expert center with sufficient experience to assess and treat these cases

Definitions:

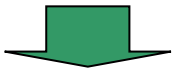
- **Absolutely cisplatin-refractory:**
  Progression while on cisplatin-based chemotherapy

- **Cisplatin-refractory:**
  Progression within 4 weeks after completion of cisplatin-based chemotherapy

- **Wider definition for refractory disease:**
  Patients after failure of salvage high dose chemotherapy or several cisplatin-based regimens

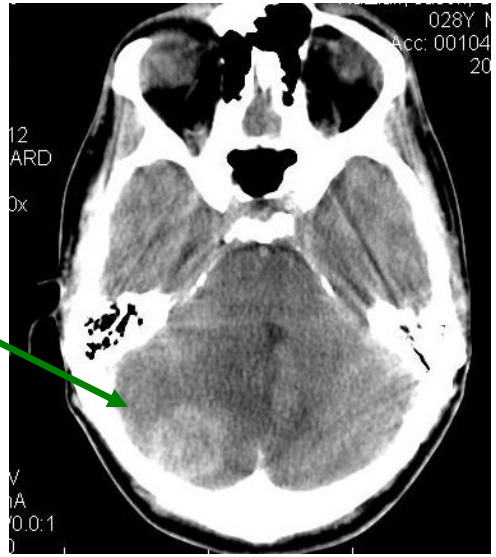
Refractory GCT: case 1

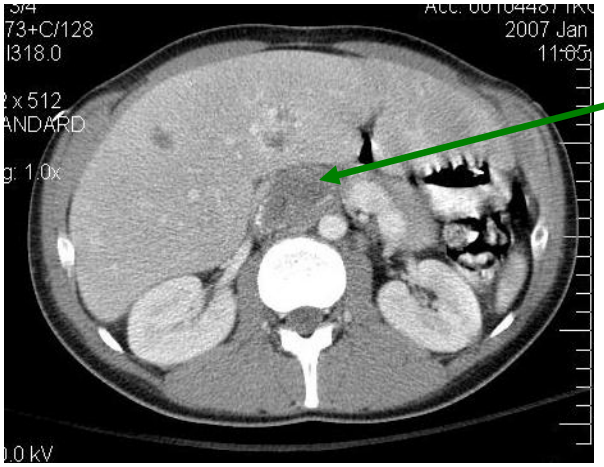
- 28 year old pt
- 1/2007: respiratory distress
- CT: lung, liver, retroperitoneal and brain metastases
- US: 10 cm testicular mass
- HCG > 1 000 000 AFP 200 LDH 6x ULN

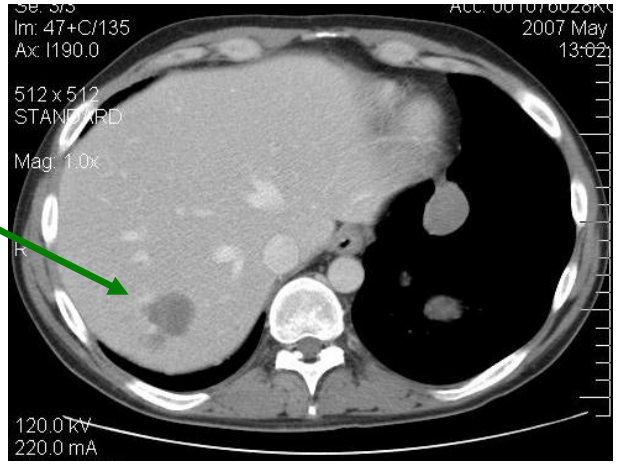


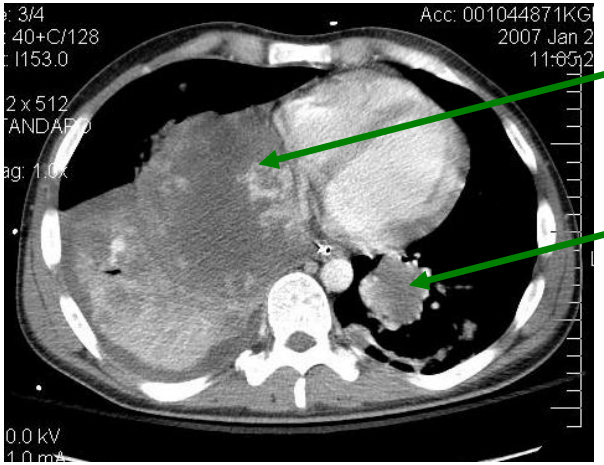
- Orchiectomy: teratoma plus choriocarcinoma

Refractory GCT: case 1







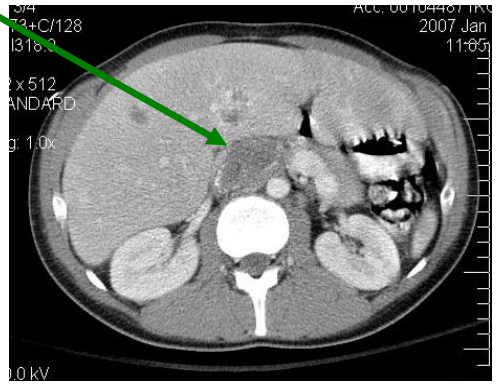


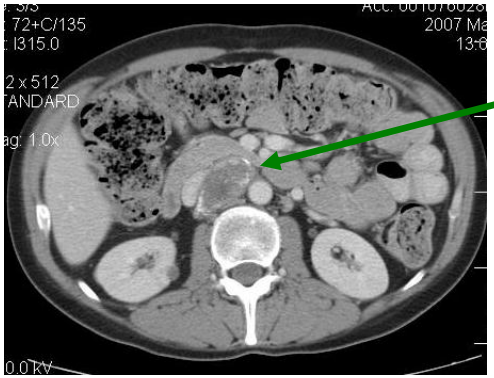
Initial diagnosis

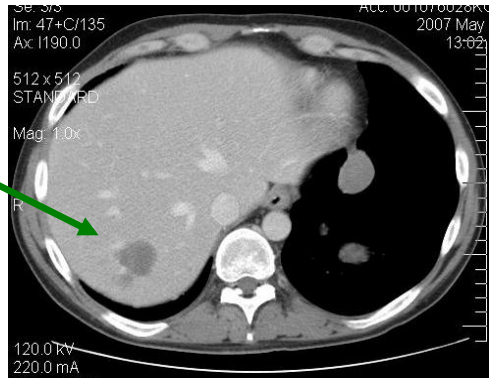
Refractory GCT: case 1

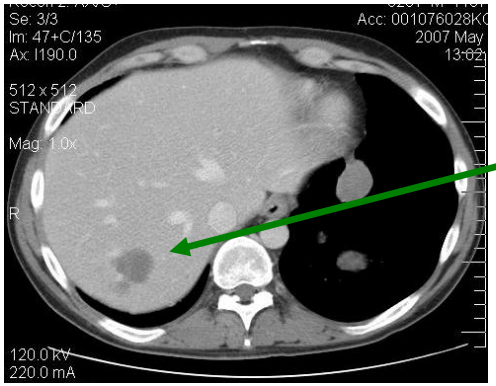
- 1/2007 – 5/2007: VIP x 4
- Resection of brain lesion during chemotherapy ⟶ necrosis
- AFP / LDH normalized HCG 13

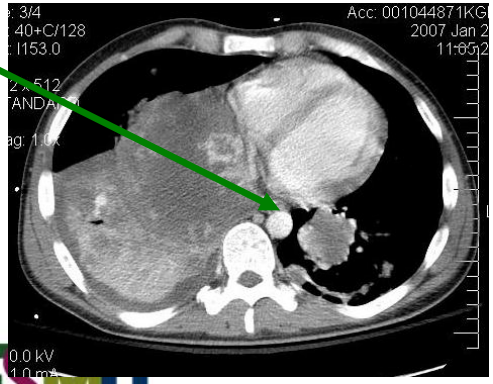
Refractory GCT: case 1

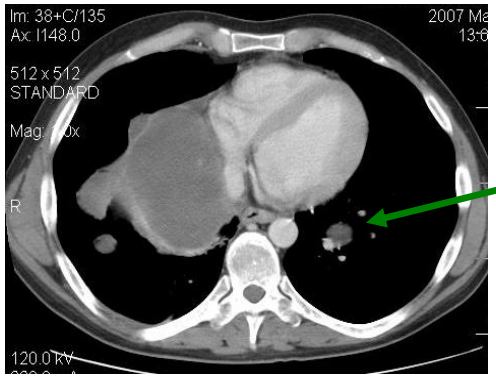












After first-line chemotherapy

Refractory GCT: case 1

Date	Time	BHCG-Quant	Reference
23 Jan, 07	15:30	> 1000000	0-5 IU/L
05 Feb, 07	10:45	223423	0-5 IU/L
15 Feb, 07	07:00	14027	0-5 IU/L
27 Feb, 07	07:35	1420	0-5 IU/L
26 Mar, 07	09:30	170	0-5 IU/L
16 Apr, 07	07:00	88	0-5 IU/L
30 Apr, 07	07:20	36	0-5 IU/L
07 May, 07	07:35	23	0-5 IU/L
10 May, 07	11:31	26	0-5 IU/L
17 May, 07	11:01	17	0-5 IU/L
24 May, 07	15:49	12	0-5 IU/L
01 Jun, 07	10:46	14	0-5 IU/L
07 Jun, 07	12:00	13	0-5 IU/L
14 Jun, 07	10:47	20	0-5 IU/L
22 Jun, 07	11:01	24	0-5 IU/L
29 Jun, 07	10:45	43	0-5 IU/L
06 Jul, 07	11:26	95	0-5 IU/L
13 Jul, 07	11:14	131	0-5 IU/L
20 Jul, 07	12:01	191	0-5 IU/L

Chemotherapy completed

Marker never normalized and increase within 4 weeks

Cisplatin-refractory !

Refractory GCT: case 1

What would you do ?

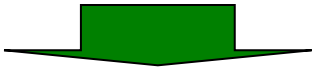
- Further diagnostics e.g. PET scan ?
- Standard dose salvage chemotherapy e.g. TIP ?
- Salvage tandem high dose chemotherapy ?
- Treatment with a non-cisplatin based regimen ?
- Resection of as much disease as possible ?

Salvage HDCT: Indiana Experience

N=184

Platinum refractory to first/second line standard chemotherapy: 21.7%

Overall cont. disease-free	116/184 (63%) after median F/U 48 months [25-112 months]
Cisplatin-refractory pts remaining disease free after HDCT	**18/40 for median F/U 49 months [22-110 months]**

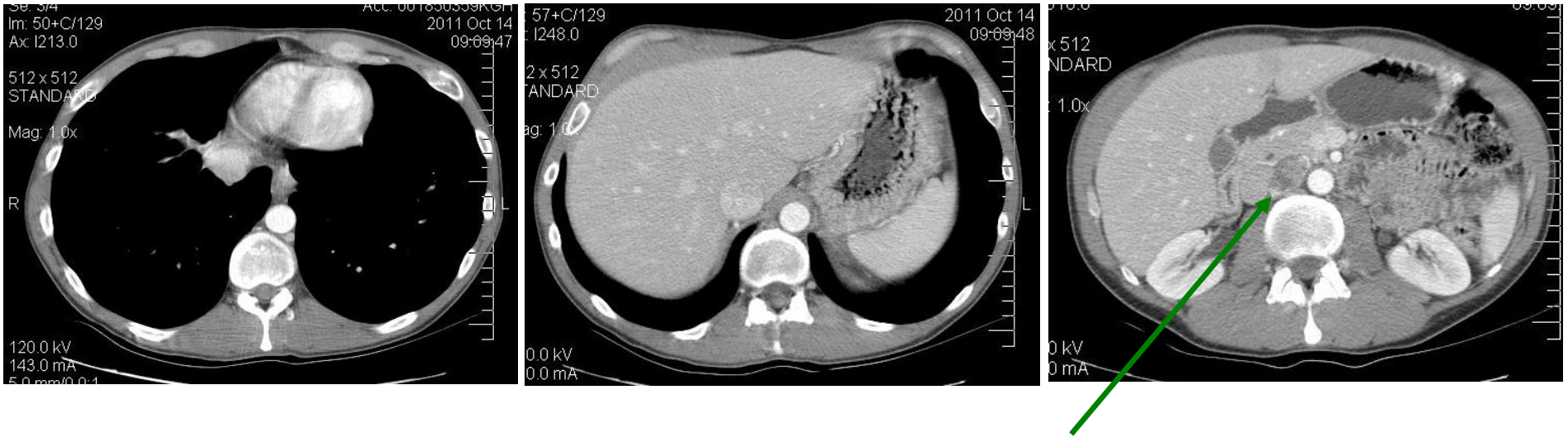


High dose chemotherapy is a good option for patients refractory to first- or second line standard dose chemotherapy

Einhorn et al NEJM 2007

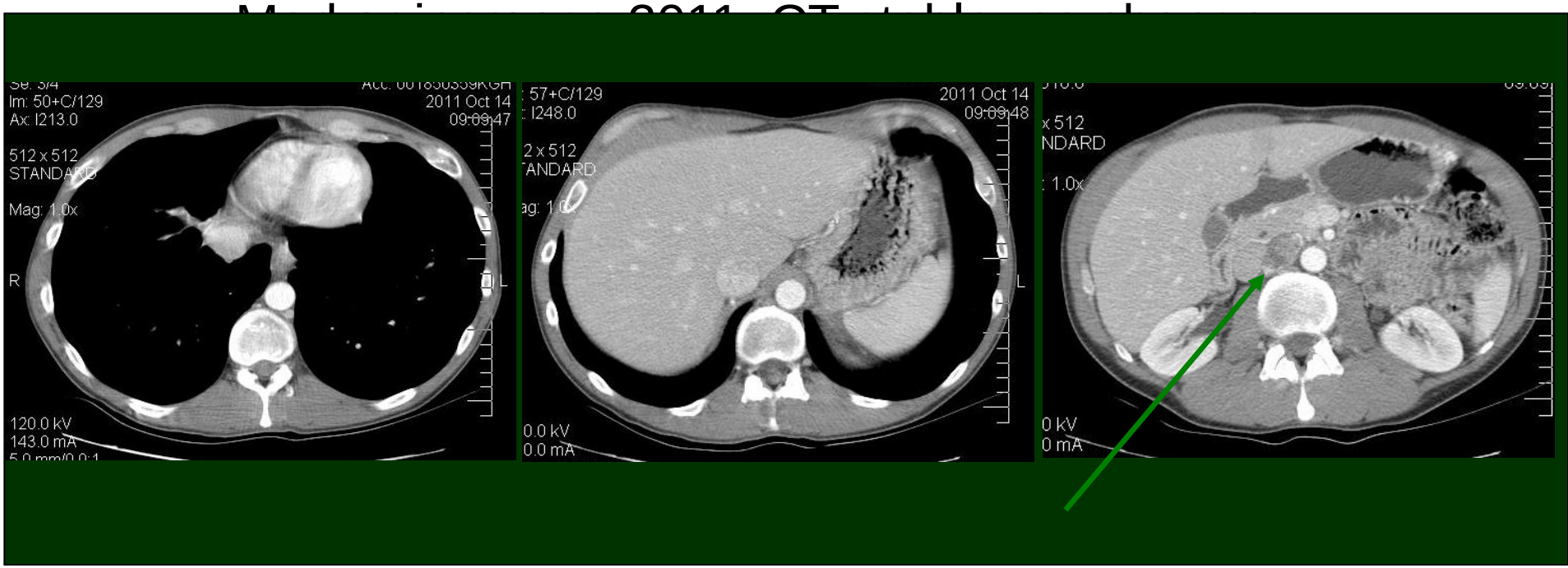
Refractory GCT: case 1

- 7/2007 – 10/2007: TIP x 2 + 2x HD-CT
- Marker normalisation
- Multiple residual sites
- No further surgery



Refractory GCT: case 1

12/2007 – 7/2011: FU / observation

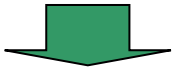


Nov 02 2011 36

Recurrence –free ever since

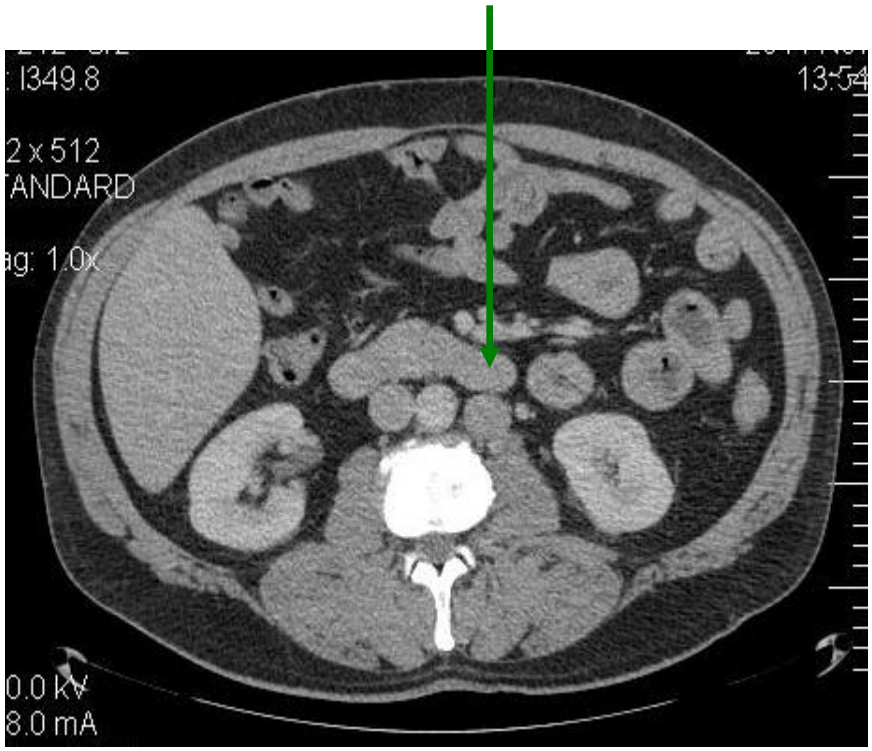
Refractory GCT: case 2

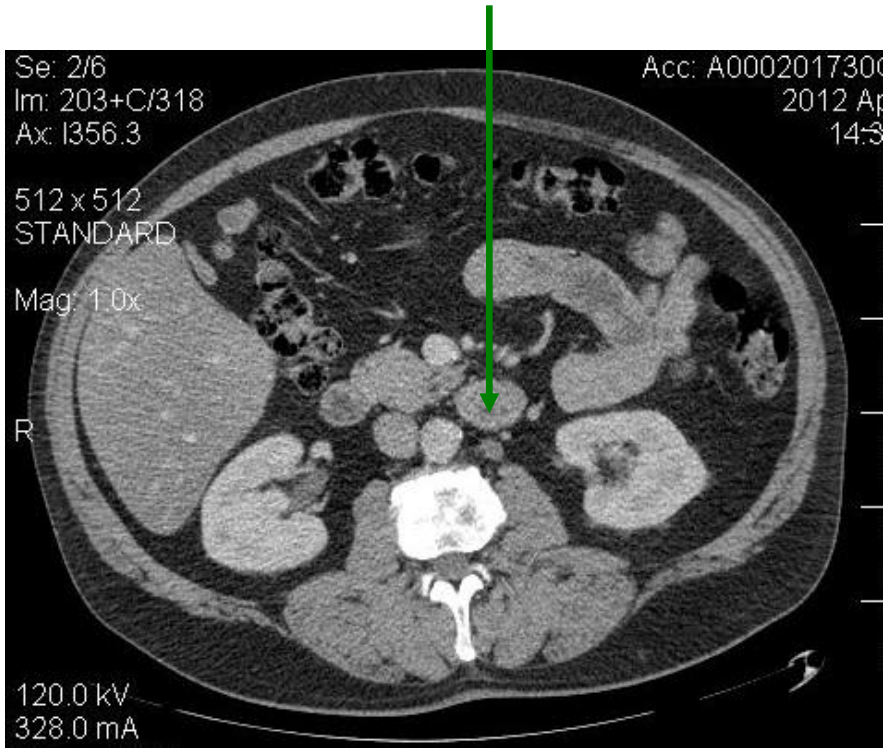
- 49 year old pt
- 11/2011: testicular mass, painless
- HCG, AFP and LDH normal
- US: 6 cm testicular mass
- CT: 2.5 cm retroperitoneal lymph node metastasis



Orchiectomy: pure seminoma

Refractory GCT: case 2



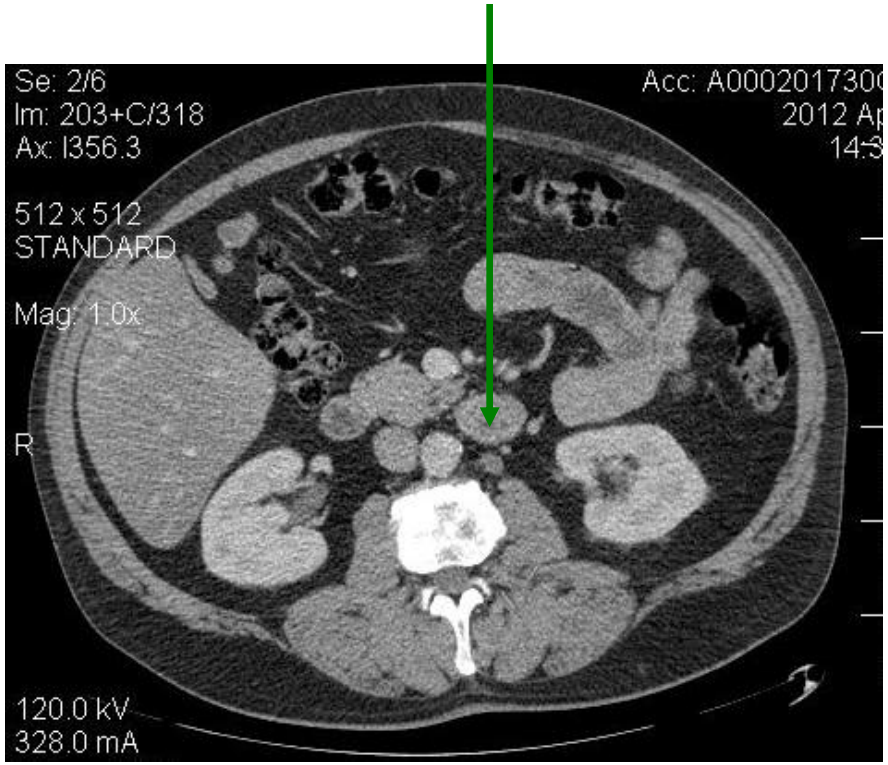


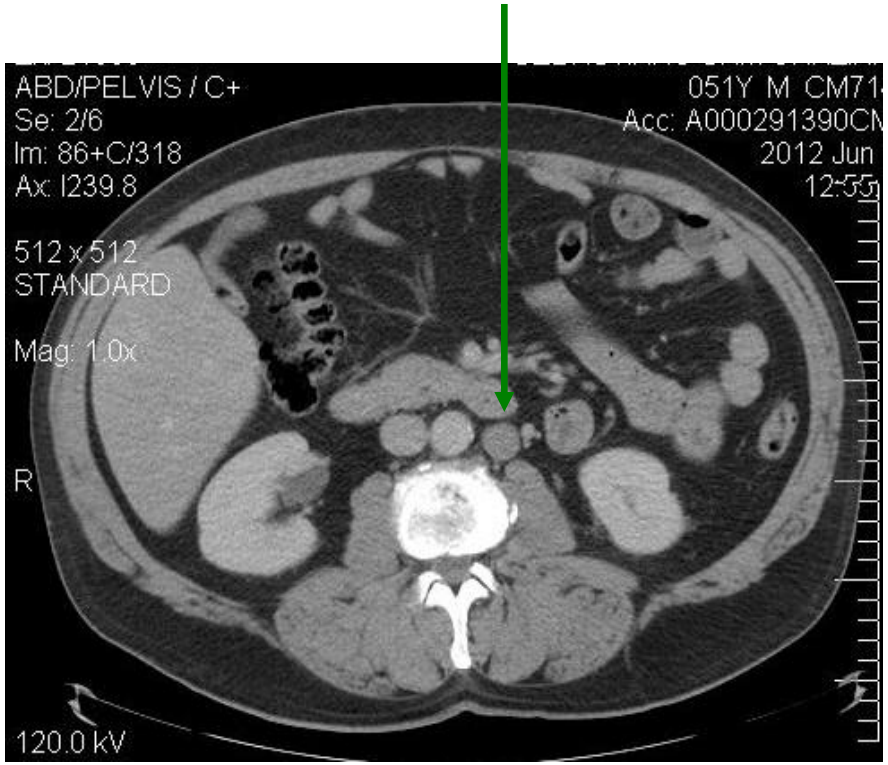
January 2012

April 2012

EP x 4

Refractory GCT: case 2





April 2012

June 2012

Early progression

Refractory GCT: case 2

What would you do ?

- Further diagnostics e.g. PET scan ?
- Standard dose salvage chemotherapy e.g. TIP ?
- Salvage tandem high dose chemotherapy ?
- Treatment with a non-cisplatin based regimen ?
- Resection of the growing lesion ?
- Radiation of the growing lesion ?

Salvage ("desperation") surgery

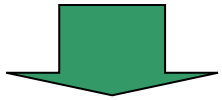
- N = 48
- Surgery for chemo-refractory disease
- RPLND x 33, thoracotomy x 6, thoracoabdominal x 3, multiple asymchronous resctions x 6
- 79% grossly rendered disease –free with 60% achieving serologic compolete remission
- 10 pts (21%) continuously disease -free
- 6 additional pts disease free after additional therapy

Potentially curative approach

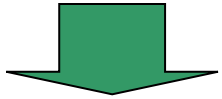
Murphy et al JCO 1993

Refractory GCT: case 2

Patient underwent RPLND



Pure vital seminoma



Recurrence free ever since

Prognosis of Refractory Patients after Salvage High-dose Chemotherapy

- Appr. 50 % of pts. will receive palliative chemotherapy after relapse from high-dose chemotherapy
- RR < 20 %
- Median survival: 8-12 months for treated pts vs. 3 months for untreated pts
- Historically 5 % long term remissions: resection ± chemotherapy
- Only significant prognostic factor:
  Interval HD-Ctx → post-HD-Ctx < 12 months (p = 0.04)

  Porcu / Einhorn J Clin Oncol 2000
- Only over the past 5-8 years recommendations based on small clinical studies with new agents

Drugs with minor / no activity in refractory GCT

Williams 1985	Mitoxantrone
Drasga 1987 / Murphy 1992	Ibroplatin
Harstrick 1990 / Stoter 1992	Epirubicin
Hoskins 1990	Mitomycin C
Motzer 1993	Suramin
Puc 1995	Topotecan
Kollmannsberger 2000	Bendamustin
Kollmannsberger 2002	Irinotecan
Kondagunta 2004	Temozolamide
Oechsle 2007	Capecitabine

Kollmannsberger / Bokemeyer Exp Opinion Pharm 2008

Chemotherapy of patients with cisplatin-refractory GCT

Agent	RR
Oral etoposide[1]	20%
Paclitaxel[2]	21%
Gemcitabine[3]	19%
Oxaliplatin[4]	19%

Combinations	RR
Paclitaxel/Gemcitabine[5]	21%
Gemcitabine/Oxaliplatin[6]	46%
Gemcitabine/Oxaliplatin[7]	32%

All studies with long-term survivors, in particular after complete resection of residual lesions

[1]Einhorn JCO 1991
[2]Motzer JCO 1994
[3]Einhorn JCO 1999
[3]Bokemeyer JCO 1999
[4]Kollmannsberger JCO 2002
[5]Hinton JCO 2002
[6]Kollmannsberger JCO 2004
[7]Pectasiadis Ann Oncol 2004

Long term outcome after chemotherapy for refractory germ cell tumors

2 GTCSG studies: Gemcitabine/Oxaliplatin (GO) and Gemcitabine/Oxaliplatin/Paclitaxel (GOP)

- N = 76 (35 GO and 41 GOP)
- Median survival for all patients: 8 months
- 8/76 alive > 2 years (11%)
- 1 GO and 7 GOP patients are relapse free with a OS > 33 mo
- All but one had chemotherapy plus subsequent surgery

Approx. 10% of patients may be cured

Surgery is a critical component of the overall treatment strategy

Kollmannsberger / Bokemeyer et al JCO 2004;
Bokemeyer / Kollmannsberger et al Ann Oncol 2008;
Ochsle / Kollmannsberger / Bokemeyer et al Eur Urol 2011

Salvage ("desperation") surgery

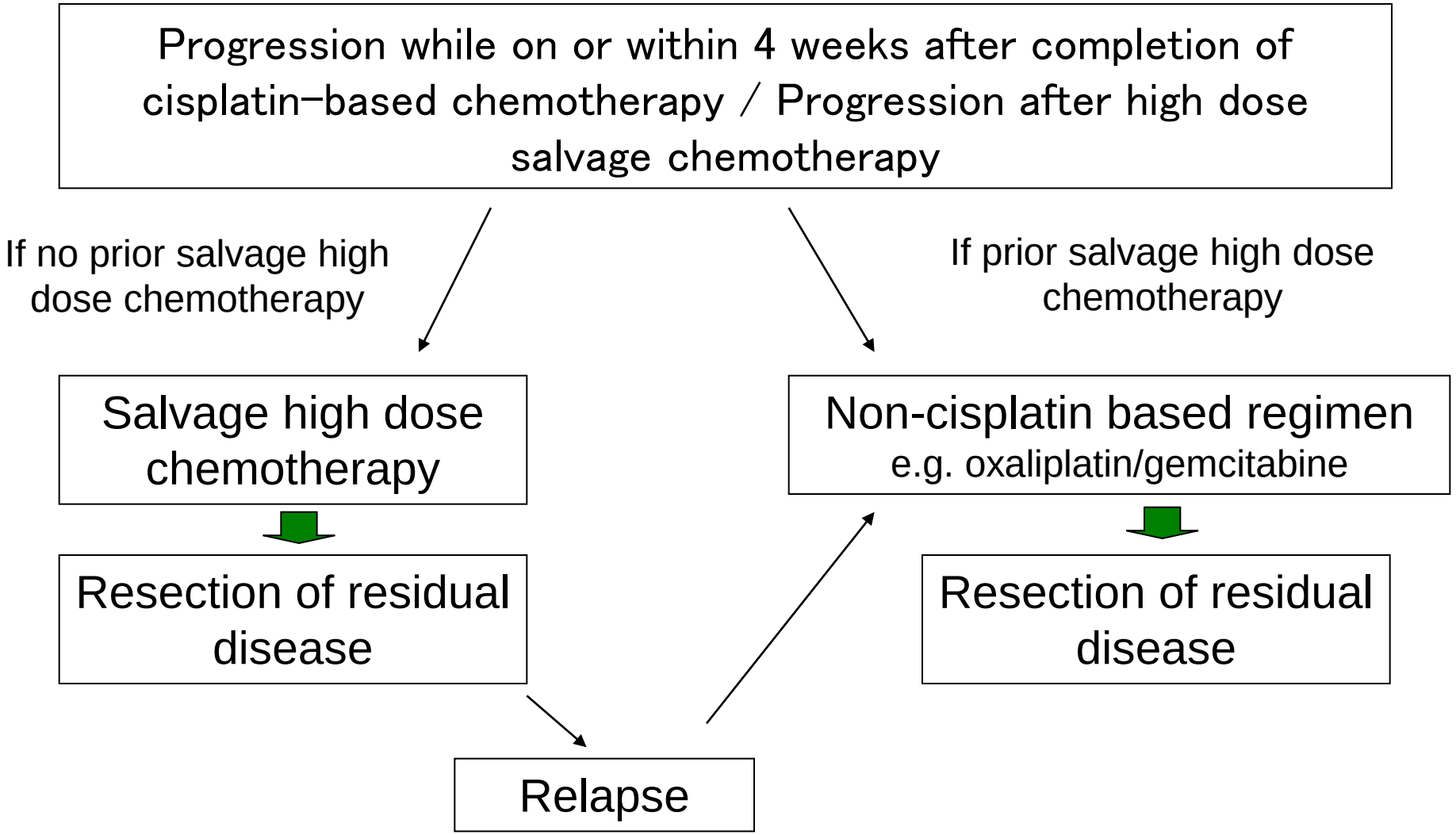
- Surgery for chemo-refractory disease
- Declining or persistent tumor markers after chemotherapy
- Slowly rising markers after initial response to chemotherapy
- Rising markers with resectable disease after exhausting all chemotherapy options
- Platinum refractory patients with resectable disease

Complete resection most important single parameter for favorable outcome

Up to 50% long term survivors

Albers et al J Urol 2000
Beck et al Urol Clin N Am 2007

Treatment of refractory GCT



Conclusions

- Patients with cisplatin refractory disease exhibit a very poor prognosis and should be considered for clinical trials
- Surgery remains an essential part of any treatment strategy for cisplatin–refractory disease or late recurrences
- The identification of new active drugs remains a priority
- The increasing understanding of the pathogenesis, and molecular changes in testicular cancer as well as of cisplatin resistance will translate into improvements in treatment and prognosis for our patients.
- International cooperation is needed to test new strategies
- Due to the complexity of relapsed GCT and the need for experienced multidisciplinary teams, patients should be treated at experienced centers !

Definition of Late Relapse

- Different definitions / patient populations exist:
  - Inclusion of “late” relapse in stage I nonseminomas
  - Inclusion of “late” relapse in stage I seminomas
  - Inclusion of late relapse of extragonadal GCT
  - Exclusion of late relapse from extragonadal GCT
  - …….

Dieckmann et al J Urol 2005; Oldenburg et al Brit J Cancer, 2006; Shahidi et al Cancer 2002; Baniel et al J Clin Oncol 1995; George et al Clin Oncol 2003; Gerl et al Ann Oncol 1997;

Late Relapse

Treatment of Chemotherapy-Naive Patients

- Stage I seminoma (surveillance, adjuvant RT, carboplatin)
- Stage IIA seminoma (RT)
- Stage I Non seminoma (RPLND or surveillance)
- Stage II nonseminoma RPLND without adjuvant chemotherapy

Cisplatin based chemotherapy (VIP / TIP / VeIP…) and surgery of residual disease

Very good prognosis

Warde et el J Urol 1997; Baniel et al JCO 1995; George et al JCO 2003; Ronnen et al JCO 2005; Sharp et al JCO 2008

Late Relapse
Characteristics

Definition: Recurrences at least 2 years after successful first-line treatment for metastatic disease

- 1–4% of pts develop late recurrences
- Incidence in nonseminoma (3–4%) > seminoma (1–2%)
- Retroperitoneum is most common location (> 50%)
- Lung (nonseminoma) and mediastinum (seminoma) are second most common location
- Time to relapse varies greatly (2–40 years)
- 60–70% are diagnosed because of symptoms
- Elevated AFP common (70%), HCG rarely elevated

Oldenburg et al JCO 2006; George et al JCO 2003; Shahidi et al Cancer 2002

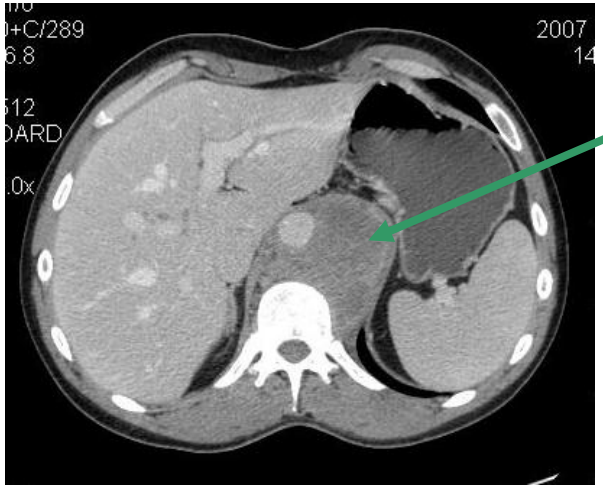
Late Relapse: Case 1

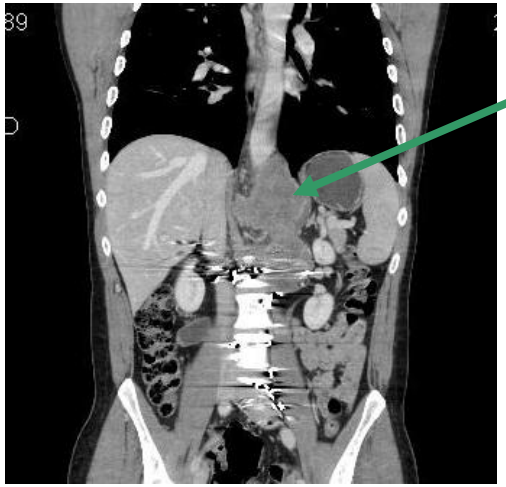
- 37 year old patient
- Initial dx at age 16 with disseminated nonseminoma, poor risk with liver, lung, retroperitoneal metastases
- Initial therapy: Cisplatin-based chemotherapy + RPLND.
- 2002: intermittent abdominal cramps, CT normal
- Intermittent abdominal pain till 2006
- Sept. 2006: CT abdo-pelvis ⟶ no abnormalities

Late Relapse: Case 1

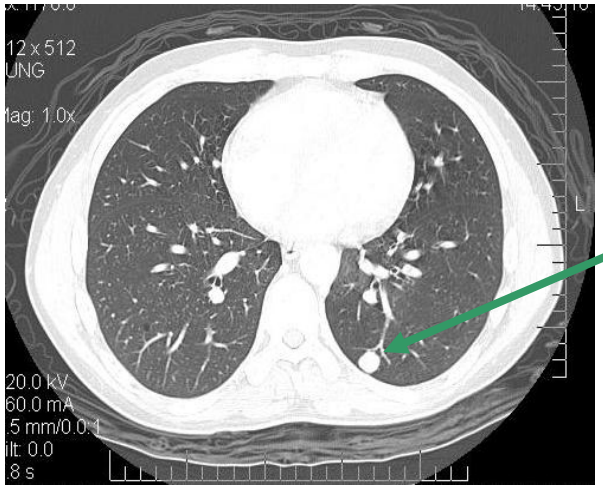
- March 2007: Pain constant, now nausea, weight loss
- U/S: large mass around aorta
- TUM April 4th: AFP 180 000, LDH 335 (ULN 220), HCG, CEA, CA19-9 normal
- CT Chest/abdo/pelvis

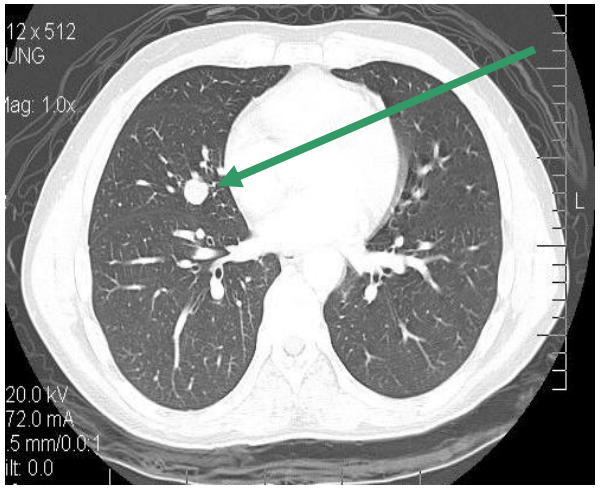
Late Relapse: Case 1





Large retrop. tumor



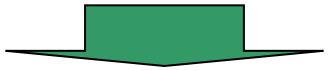


Multiple Lung metastases

April 2007

Late Relapse
Differential Diagnosis

- Metastases from a new contralateral primary
- A new primary EGGCT
- Metastases from a new non-GCT primary
- Transformed teratoma
- Growing teratoma



Biopsy required if not resectable !!

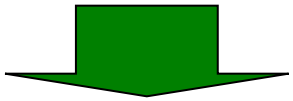
Nichols CR Semin Surg Oncol 1999

Late Relapse: Case 1

- New primary GCT ????
  - US testicle entirely normal
- Other malignancy ?
  - But AFP high
  - Unlikely at that age
  - Biopsy

Late Relapse
Pathology

- Teratoma most common
  - Can "leak" low amounts of AFP/HCG
- Yolk Sac most common active germ cell subtype but can have atypical appearance
- All other GCT subtypes are possible
- Transformed teratoma (5–15%)
  - Sarcomas, adenocarcinomas, undifferentiated carcinoma



- If in doubt ⟶ test for presence of i(12p)
- expert pathology review recommended

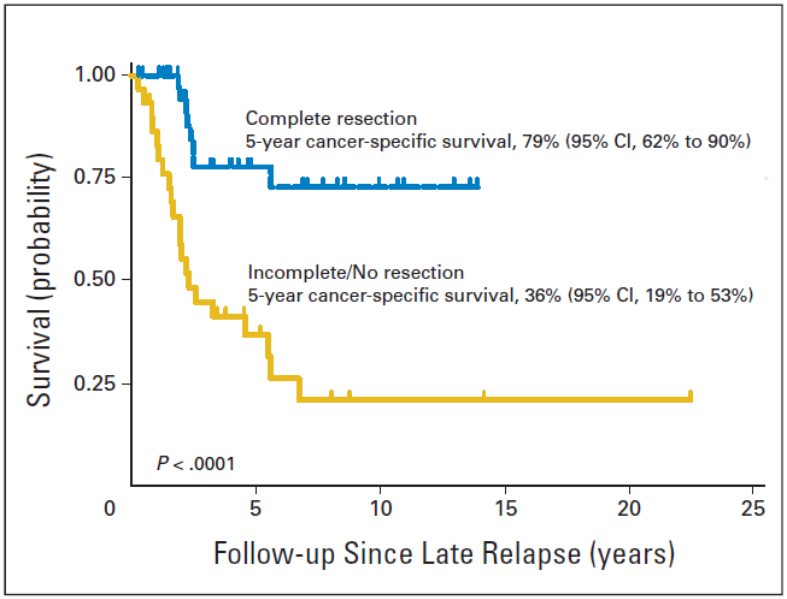
Michael et al Am J Sur Path, 2000

Late Relapse: Case 1

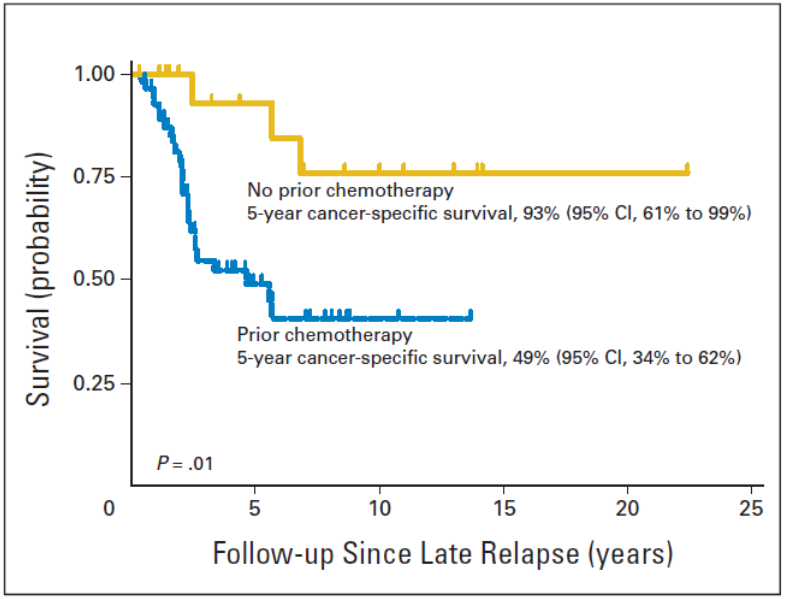
- Biopsy: embryonal carcinoma/Yolk Sac
- What would you do ?
  - Treatment with VIP (Etoposide/Ifosfamide/Cisplatin)
  - Treatment with BEP (Bleomycin/Etoposide/Cisplatin)
  - Treatment with a non-cisplatin containing regimen e.g. oxaliplatin/gemcitabine
  - High dose chemotherapy

Late Relapse

Adverse Prognostic Factors



Complete vs. incomplete resection



Prior CTx vs. no prior Ctx

Symptoms at presentation and multifocality are associated with a poor prognosis

Sharp et al JCO 2008

Management – Chemotherapy

- Chemotherapy is given according to histology
  - Platinum based chemotherapy (e.g. TIP) for germ cell histologies

Ronnen et al JCO 2005

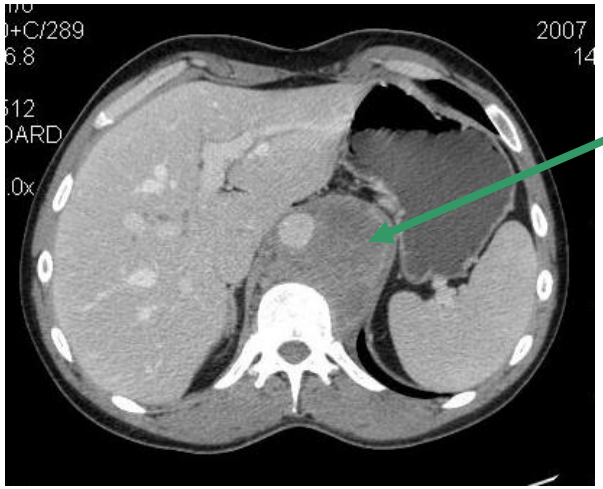
- Frequently chemotherapy-resistant
- High-dose chemotherapy remains controversial
  - Very few data
  - Long-term survivors rare but have been reported
  - Resection as an important part of the overall treatment strategy

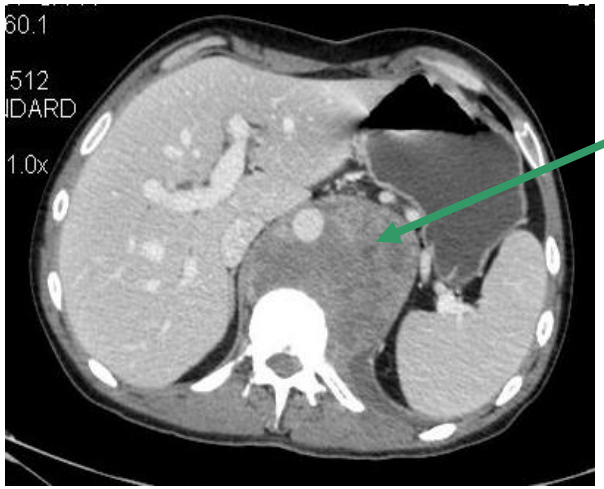
Lorch et al Ann Oncol 2010

- Responses to chemotherapy are infrequent and usually short-lived
- Chemotherapy alone (without surgery) induced long-term survival is extremely rare

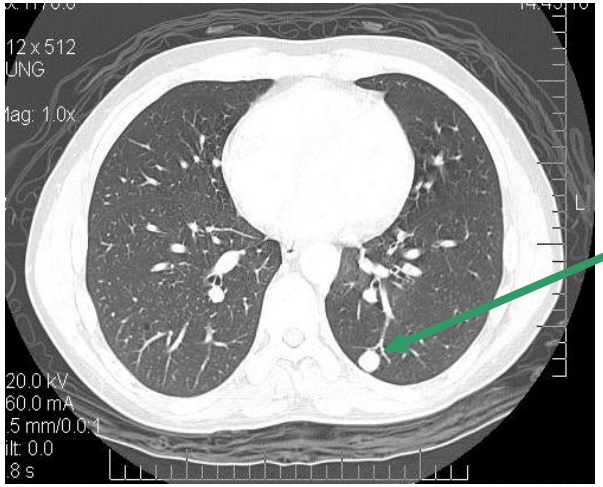
Late Relapse: Case 1 – Staging after 2 Cycles

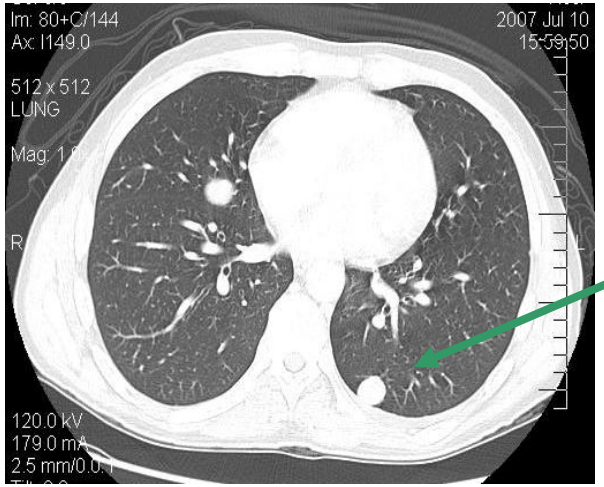
April 2007





June 2007

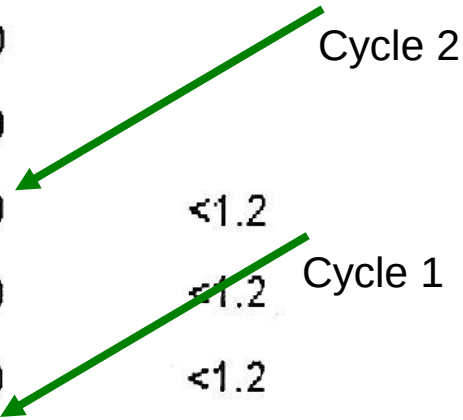




VIP x 2

Late Relapse: Case 1- Staging after 2 Cycles VIP

Spec. ID	Collection Date	Specimen Type	AFP ug/L	B-hCG IU/L
L90605	30-May-2007	Serum	370000	
L86422	22-May-2007	Serum	360000	
L88112	14-May-2007	Serum	320000	
L87327	07-May-2007	Serum	330000	<1.2
L85069	01-May-2007	Serum	320000	<1.2
L85212	01-May-2007	Serum	290000	<1.2
L79496	10-Apr-2007	Serum	170000	<1.2
L79172	04-Apr-2007	Serum	180000	<1.2



Late Relapse: Case 1

- What would you do ?
  - Treatment with BEP (Bleomycin/Etoposide/Cisplatin)
  - Treatment with a non-cisplatin containing regimen e.g. oxaliplatin/gemcitabine
  - High dose chemotherapy
  - Attempt resection ?
  - Palliative care

Late Relapse

Management – Surgery

- Surgery is the most important component of treatment in patients with late-relapsing TC
  - Surgical resection should be aggressively pursued whenever possible
- Treatment at high volume / expert centers is highly recommended
- No adjuvant chemotherapy after complete resection
- Postchemotherapy RPLND for residual disease (> 1 cm) the most important preventative strategy

Sharp et al JCO 2008
Ronnen et al JCO 2005

Late Relapse: Case 1

- Gemcitabine/oxaliplatin x 1 cycle: May/June 2007
  - Acute severe neuropathic reaction day 1 to oxaliplatin
- Gemcitabine 2 cycles

H22304	SERUM	23-Aug-2007	460000	
F3360	SERUM	10-Aug-2007	370000	**Gemcitabine**
W3484	SERUM	11-Jul-2007	490000	
W74825	SERUM	20-Jun-2007	540000	

Late Relapse: Case 1

- What would you do ?
  - Treatment with BEP (Bleomycin/Etoposide/Cisplatin)
  - Treatment with different non-cisplatin containing regimen e.g. paclitaxel
  - High dose chemotherapy
  - Clinical trial
  - Palliative care

Late Relapse: Case 1

Acc #	Spec Type	Coll Date	AFP ug/L
M28249	SERUM	24-Dec-2007	250000
W76743	SERUM	28-Nov-2007	170000
H61442	SERUM	01-Nov-2007	490000
M6717	SERUM	29-Oct-2007	380000
T53503	SERUM	[illegible]	00
M80264	SERUM	12-Oct-2007	520000
W43315	SERUM	26-Sep-2007	580000
W39630	SERUM	19-Sep-2007	380000
T33239	SERUM	11-Sep-2007	300000
H22304	SERUM	23-Aug-2007	460000
F3360	SERUM	10-Aug-2007	370000
W3484	SERUM	11-Jul-2007	490000
W74825	SERUM	20-Jun-2007	540000

- **DOD March 2008**

Start sunitinib

Late Relapse: Case 2

- 38 year old pt
- 2002: good prognosis NS
- AFP 459, HCG normal, LDH normal
- CT scan: retroperitoneal LN 4 cm

Orchiectomy: Yolk Sac, Embryonal carcinoma , Teratoma

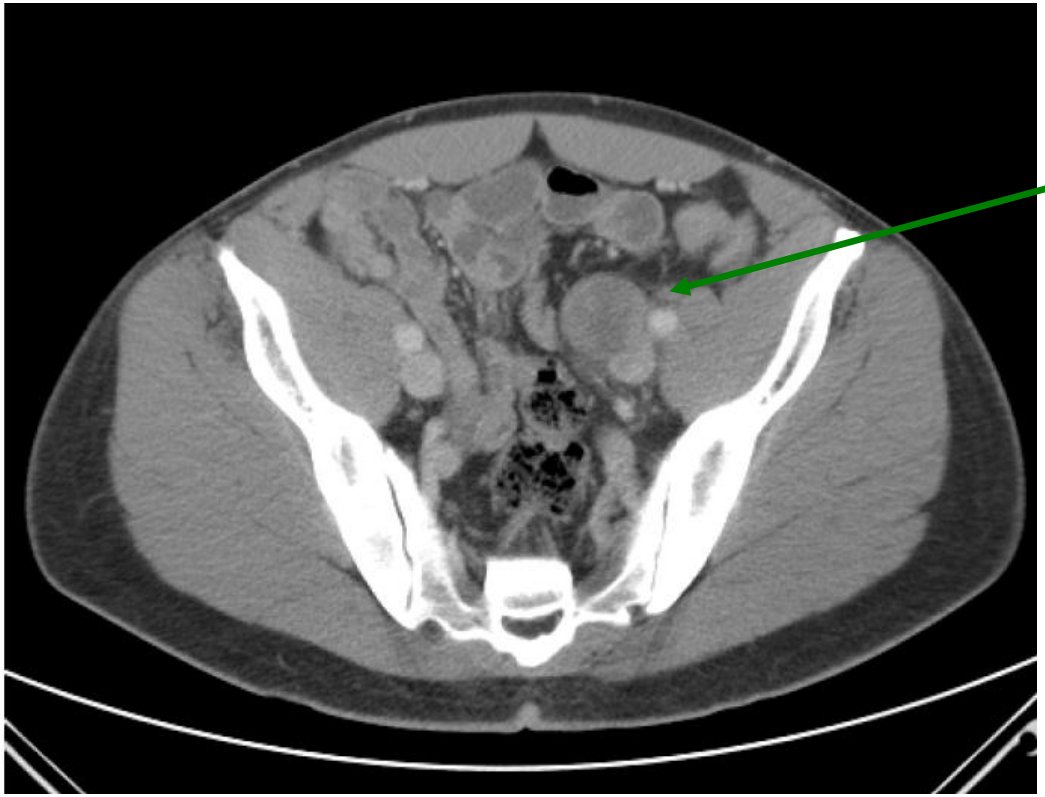
BEP x 3 → marker negative PR

RPLND: Mature Teratoma, completely resected

Late Relapse: Case 2

Recurrence –free until 2011

2011: AFP 3100



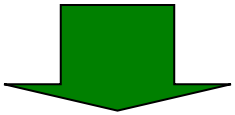
Isolated pelvic lymph node

Late Relapse: Case 2

- What would you do ?
  - Treatment with VIP or TIP
  - Treatment with a non-cisplatin containing regimen e.g. oxaliplatin/gemcitabine
  - High dose chemotherapy
  - Resection of disease
  - Palliative care

Late Relapse: Case 2

Resection: left and right-sided pelvic, paracaval, and periaortic LAD



Pathology: solitary lymph node, Yolk Sac histology

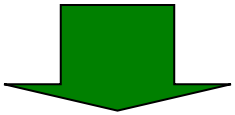
no other nodes involved

Late Relapse: Case 2

- What would you do ?
  - Treatment with standard dose cisplatin-based chemotherapy x 4 cycles e.g. VIP ?
  - Treatment with standard-dose cisplatin-based adjuvant chemotherapy x2 cycles ?
  - Treatment with different non-cisplatin containing regimen e.g. paclitaxel ?
  - High dose chemotherapy ?
  - Watch without further therapy ?

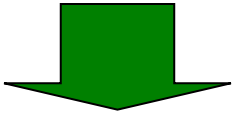
Late Relapse: Case 2

Resection: left and right-sided pelvic, paracaval, and periaortic LAD



Pathology: solitary lymph node, Yolk Sac histology

no other nodes involved

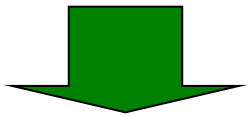


Recurrence free since

Late Relapse

Treatment of marker-only disease

- PET scan to identify the site of evolution in a minority of patients
- Detection by CT scan in the majority of patients
- Withhold any treatment until the site of evolution is demonstrated and manageable by surgical excision



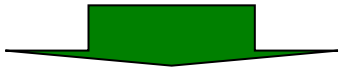
Surgery ± chemotherapy whenever feasible

Gerl et al Ann Oncol, 1997

Late relapse

Malignant Transformation

- Rare, estimated to occur in 3–6% of pts with teratoma components
- Limited literature, mostly small series
- Poor prognosis
- Treatment according to histology
- Cisplatin-based GCT chemotherapy of limited benefit



Resection **as the treatment of choice whenever possible**

CONCLUSION (1)

- Late relapse is rare (< 5% in modern series)
- More frequent in advanced non seminoma
- Importance of postchemotherapy resection of residual disease:
  - Risk of growing teratoma
  - Risk of transformed teratoma
  - More often yolk sac tumor
- Largely resistant to chemotherapy except for chemo-naive patient
- Salvage surgery is the mainstay of therapy
- Approx. 20-60% long term survivors depending on complete resectability
- Referral to expert centers strongly recommended

CONCLUSION (1)

- Late relapse is rare (< 3–5% in modern series)
- More frequent in advanced non seminoma
- Importance of postchemotherapy resection of residual disease:
  - Risk of growing teratoma
  - Risk of transformed teratoma
  - More often yolk sac tumor
- Targeted agents have standard role in the treatment of these tumors at the present time

CONCLUSION (2)

- Largely resistant to chemotherapy except for chemo-naive patient
- Salvage surgery is the mainstay of therapy
- Approx. 20-60% long term survivors depending on complete resectability
- Referral to expert centers strongly recommended