European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

16th February 2022

Andrada Turcas & Norbert Graf

SECOND, PECULIAR RECURRENCE OF A WILMS TUMOR: PLEURAL AND LATE

Moderation: Teresa de Rojas

Special guest: Anita Kienesberger

Co-funded by the European Union's Health Programme

SIOPE YOUNG

St. Anna Kinderkrebs Forschung

COI declaration

- None

Timeline

Diagnosis
Dec. 2010

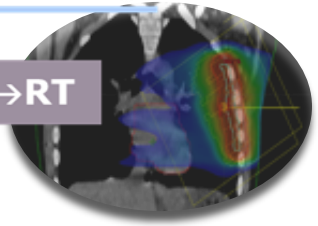
Jun. 2011
ChT→ Surgery →ChT

Pulmonary Metastasis
May 2012

ChT

Pleuro-Pulmonary Relapse
Feb.2021

May-Jul 2021
Surgery→ChT→RT

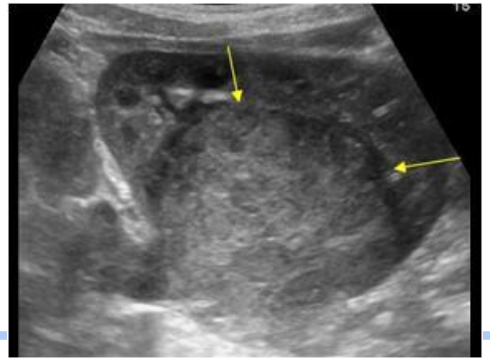


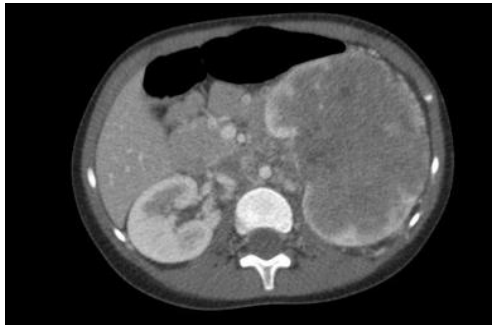
Timeline

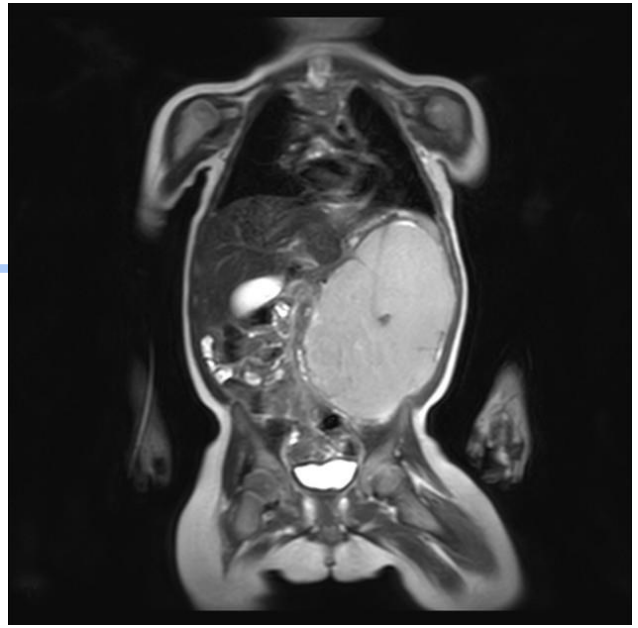
2 yo

Diagnosis

Dec. 2010







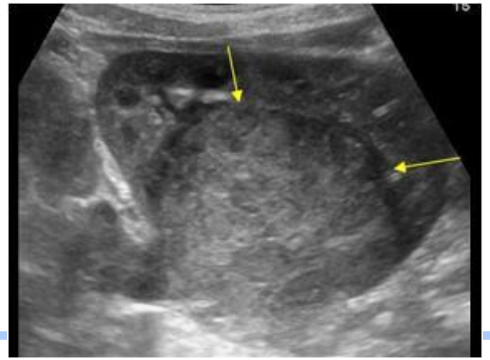
Timeline

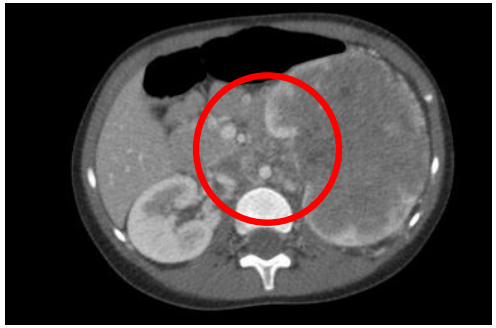
2 yo

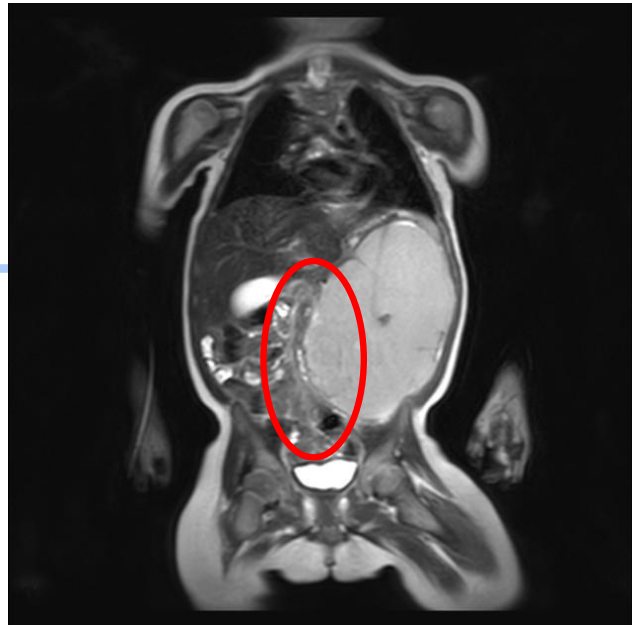
→ Left Nephroblastoma

Diagnosis

Dec. 2010







Q1: What would you do next ?

a) Multidisciplinary Tumor board discussion
b) Imaging review by an expert Paediatric Radiologist
c) Biopsy for histological confirmation
d) Upfront Surgery
e) Chemotherapy first, Surgery next

Timeline

2 yo

→ Left Nephroblastoma

Diagnosis

Dec. 2010

Dec. 2010

ChT

❑ *4w NA ChT (AV)*

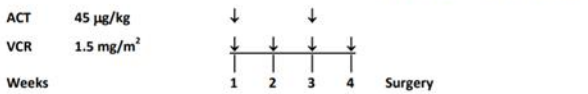
15.2.1.1 Pre-operative chemotherapy

Two drugs (vincristine (VCR) and actinomycin D (ACT)) x 4 weeks (Figure 1)

- Vincristine: 1.5 mg/m² (max 2 mg) weeks 1, 2, 3, 4 (5th dose can be given if week 5 falls before planned surgery)
- Actinomycin D: 45 µg/kg (max 2 mg), weeks 1, 3

Both drugs are given by intravenous bolus.

SIOP 2001



Timeline

2 yo

→ *Left Nephroblastoma*

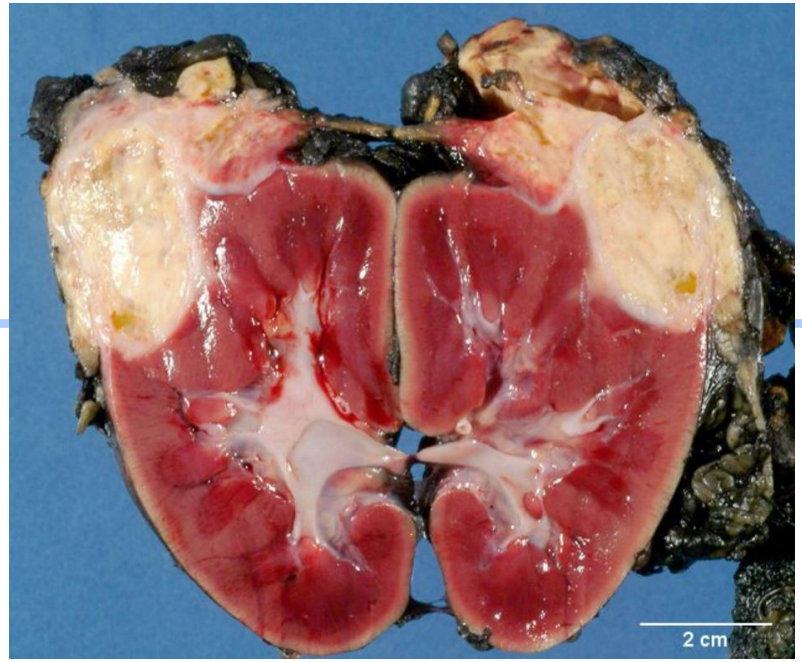
Diagnosis

Dec. 2010

Jan. 2011

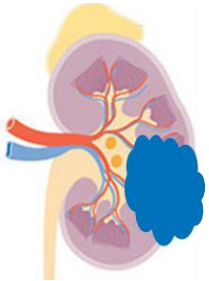
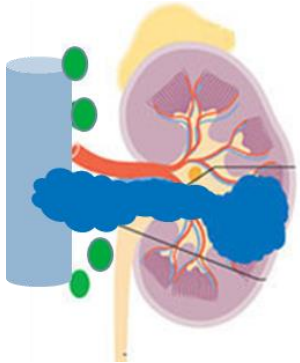
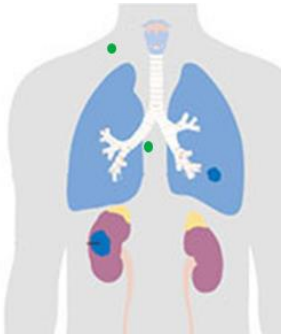
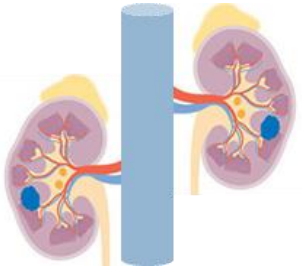
ChT→ Surgery

- *4w NA ChT (AV)*
- ***Total Nephrectomy***



https://www.webpathology.com/image.asp?case=73&n=6

Staging

I	II	III	IV	V
				
45%	20%	20%	10%	5%

http://www.urologist.com.sg/urology-problem/kidney-cancer.html

Risk groups

Current SIOP classification of paediatric renal tumours

Pre-treated tumours*	Primary nephrectomy tumours
Low risk	Low risk
Mesoblastic nephroma	Mesoblastic nephroma
Cystic partially differentiated nephroblastoma	Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma	
Intermediate risk	Intermediate risk
Nephroblastoma – epithelial type	Non-anaplastic nephroblastoma and its variants
Nephroblastoma – stromal type	Nephroblastoma – focal anaplasia type
Nephroblastoma – mixed type	
Nephroblastoma – regressive type	
Nephroblastoma – focal anaplasia type	
High risk	High risk
Nephroblastoma – blastemal type	Nephroblastoma – diffuse anaplasia type
Nephroblastoma – diffuse anaplasia type	Clear cell sarcoma of the kidney
Clear cell sarcoma of the kidney	Rhabdoid tumour of the kidney
Rhabdoid tumour of the kidney	

If >66% (2/3) of the tumour is non-viable (i.e., shows chemotherapy-induced changes), it is regarded as **REGRESSIVE TYPE**, irrespective of the presence of remaining viable tumour components.

Popov SD, Sebire NJ, Vujanic GM. Wilms' Tumour – Histology and Differential Diagnosis. In: van den Heuvel-Eibrink MM, editor. Wilms Tumor [Internet]. Brisbane (AU): Codon Publications; 2016 Mar. Table 2, [Current SIOP classification of paediatric renal tumours].

Timeline

2 yo

→ *Left Nephroblastoma*

Diagnosis

Dec. 2010

Jan. 2011

ChT

- ❑ *4w ChT (AV)*
- ❑ *Total Nephrectomy*

Timeline

2 yo

→ *Left Nephroblastoma*

→ ***Stg. III***
→ ***Regressive type***
→ ***Intermediate Risk***

Diagnosis

Dec. 2010

Jan. 2011

ChT

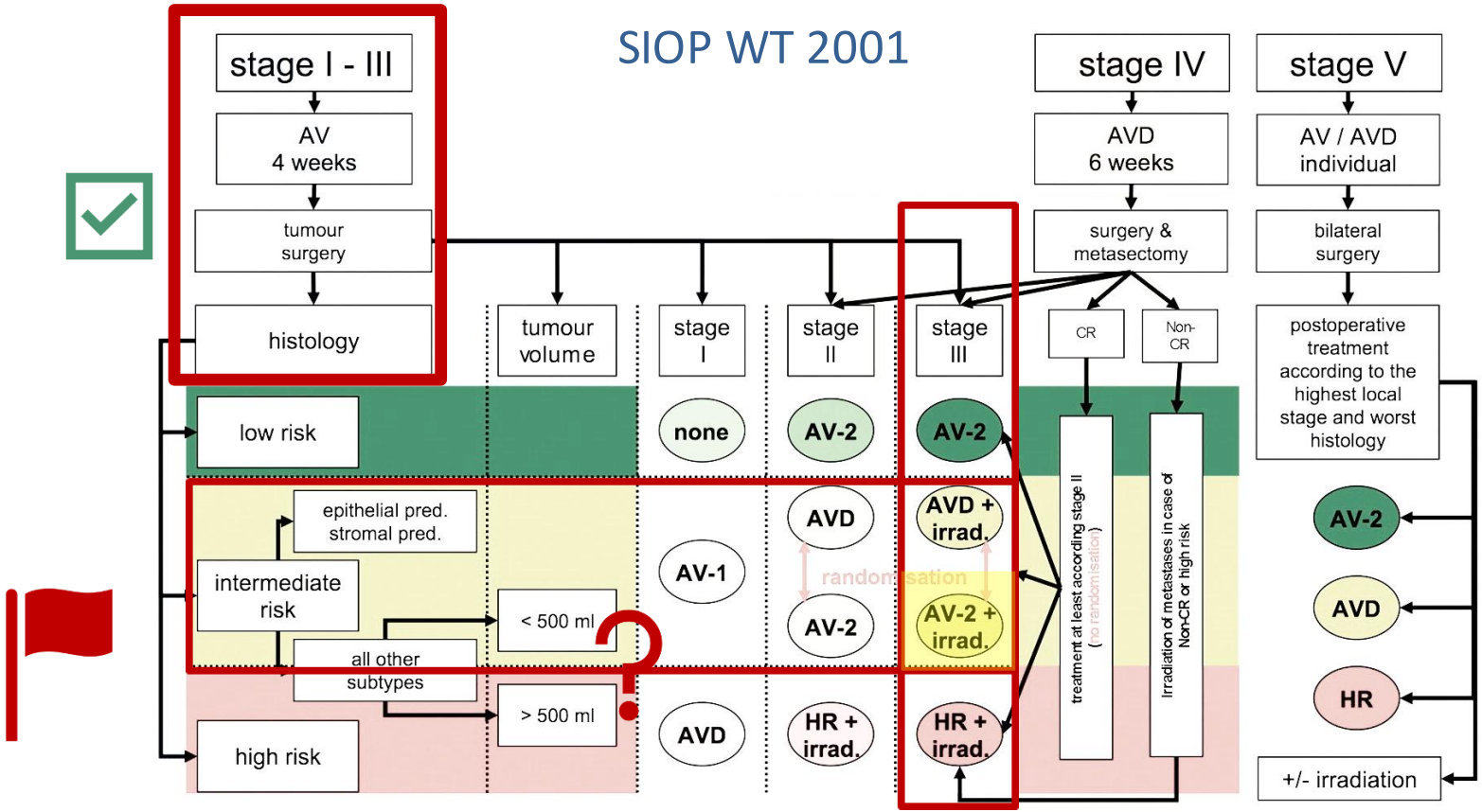
- ❑ *4w ChT (AV)*
- ❑ *Total Nephrectomy*

Q2 What would you do next?

a) Observation
b) Radiotherapy only
c) Chemotherapy only
d) Make a decision after MDT discussion
e) Chemotherapy + Radiotherapy

Treatment

SIOP WT 2001



Timeline

2 yo

→ *Left Nephroblastoma*

→ *Stg. III*

→ *Regressive type*

→ *Intermediate Risk*

Diagnosis

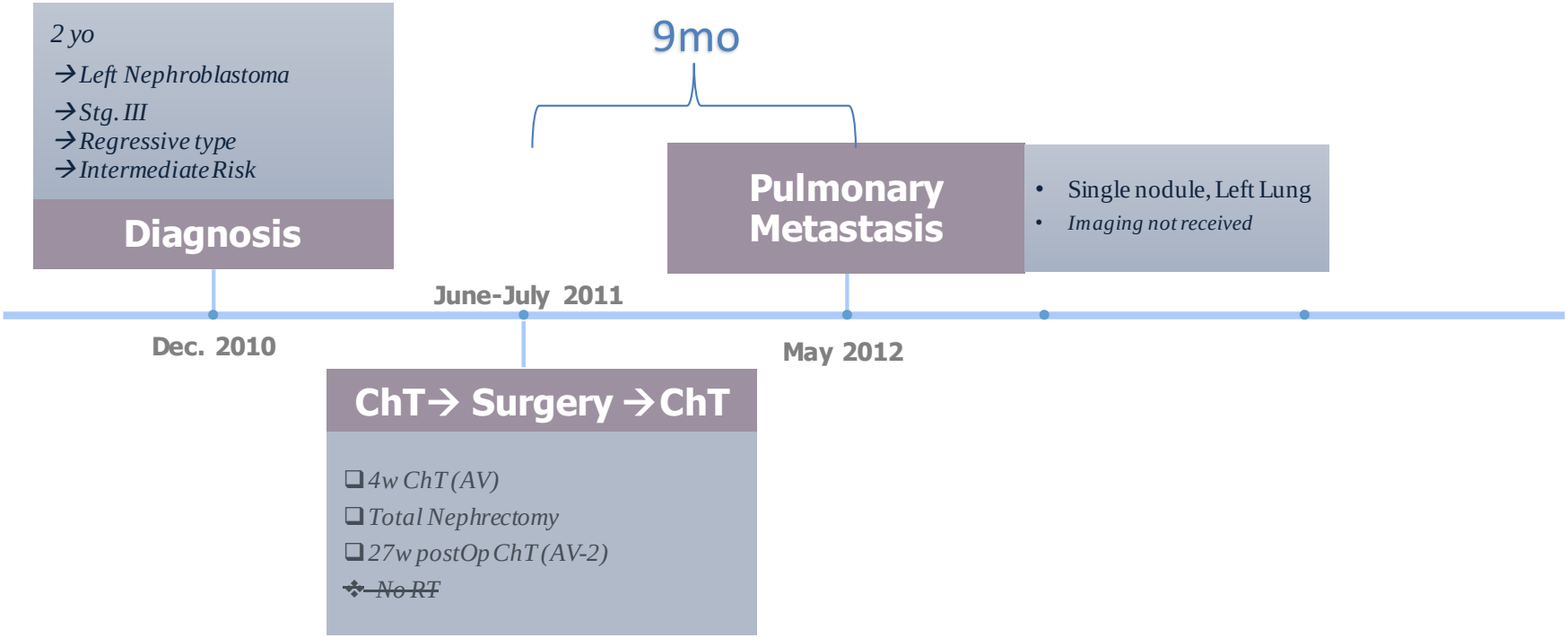
Dec. 2010

June-July 2011

ChT→ Surgery →ChT

- ❑ *4w ChT (AV)*
- ❑ *Total Nephrectomy*
- ❑ ***27w postOp ChT (AV-2)***
- ❖ ~~*No Flank RT*~~

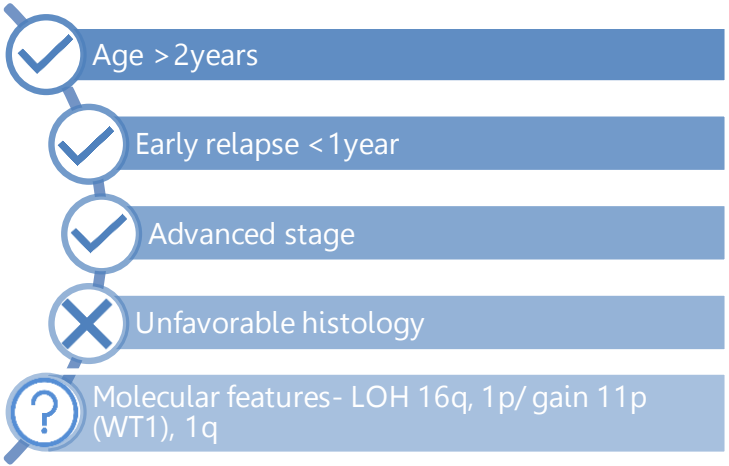
Timeline


2 yo
→Left Nephroblastoma
→Stg. III
→Regressive type
→Intermediate Risk
Diagnosis
9mo
Pulmonary Metastasis
• Single nodule, Left Lung
• Imaging not received
June-July 2011
Dec. 2010
May 2012
ChT→ Surgery →ChT
❑ 4w ChT (AV)
❑ Total Nephrectomy
❑ 27w postOp ChT (AV-2)
❖ ~~No RT~~

Relapse

- Usually occurs within 2 years form the primary
- % Pulmonary

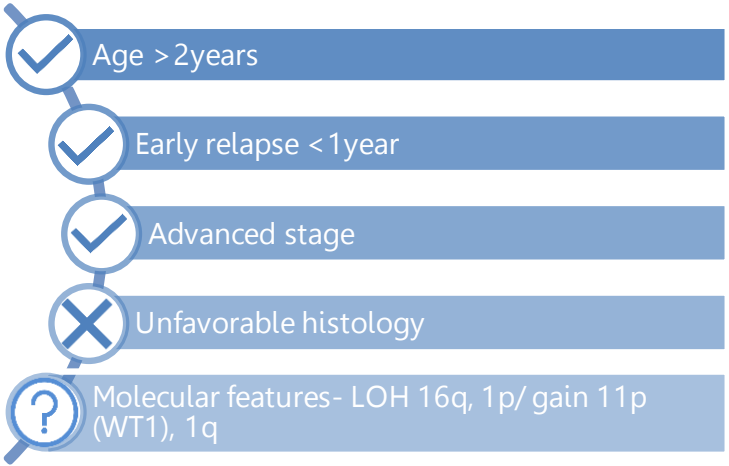
Negative Prognostic Factors



Relapse

- Usually occurs within 2 years form the primary
- % Pulmonary

Negative Prognostic Factors



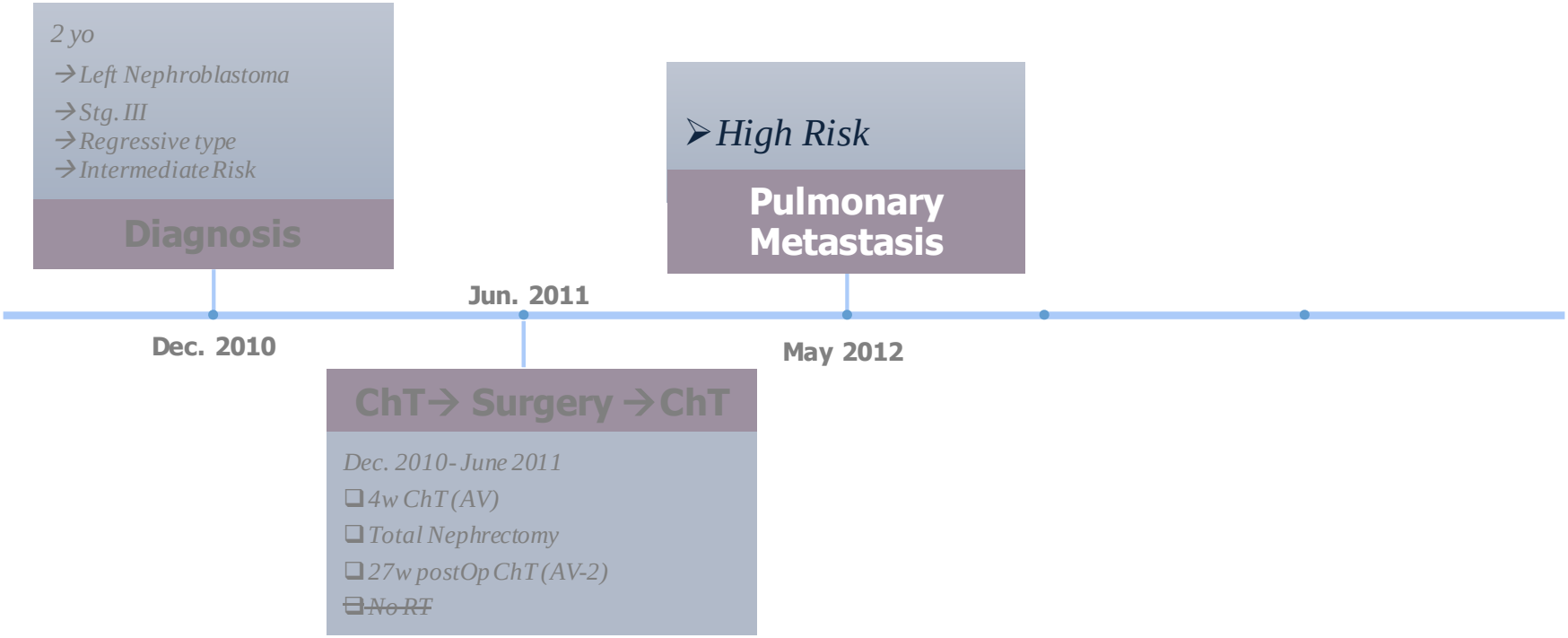
Risk group

Standard	**High**	Very High
• 30% ❑ Favorable Histology ❑ ChT (V +/A) • *EFS 70-80%* ❖ Surgery → ChT+/RT ❖ ChT+/RT	• 45-50% ❑ **Fav. Histology** ❑ >3 types of ChT ±RT ❑ **Early relapse** • *EFS 40-50%* ❖ Surgery → ChT+/RT ❖ ChT+/RT →SCR	• 10-15% ❑ Anaplastic ❑ Blastemal ❑ Early relapse • *OS<10%* ❖ *ChT!!! →SCR*

Q3: What is required next?

a) MDT to decide further treatment
b) Molecular/genetic assessment for risk stratification
c) Surgery only
d) Surgery + Chemotherapy
e) Surgery + Chemotherapy + Whole Lung RT (±Boost)

Timeline


2 yo
→Left Nephroblastoma
→Stg. III
→Regressive type
→Intermediate Risk
Diagnosis
Dec. 2010
Jun. 2011
ChT→ Surgery →ChT
Dec. 2010- June 2011
4w ChT (AV)
Total Nephrectomy
27w postOp ChT (AV-2)
No RT
➢High Risk
Pulmonary Metastasis
May 2012

Timeline

2 yo
→Left Nephroblastoma
→Stg. III
→Regressive type
→Intermediate Risk

Diagnosis

Dec. 2010

Jun. 2011

ChT→ Surgery →ChT

Dec. 2010- June 2011
- ❑ *4w ChT (AV)*
- ❑ *Total Nephrectomy*
- ❑ *27w postOp ChT (AV-2)*
- ~~❑ *No RT*~~

- ➢ *High Risk*

Pulmonary Metastasis

May 2012

ChT

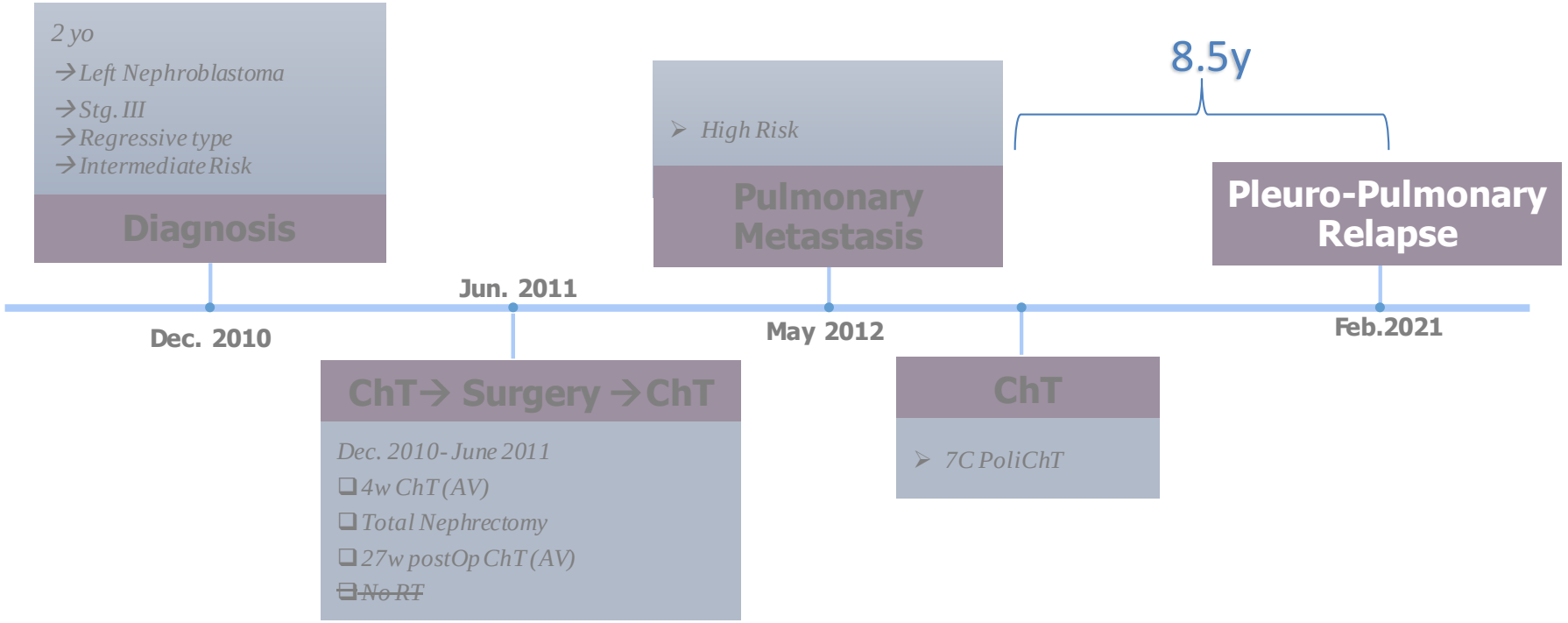
- ➢ 7 C
- 4 x Carbo/VP-16
- 3 x CPM/VP-16

Stratum C of the NWTS-5 relapse pr

Week
CTX 440 mg/m^2 X 5 d
CARBO 500 mg/m^2 X 2 d
E (VP-16) 100mg/m^2 X 5 d/ 3 d[a]

~~Surgery~~
~~WLI~~

Timeline


2 yo
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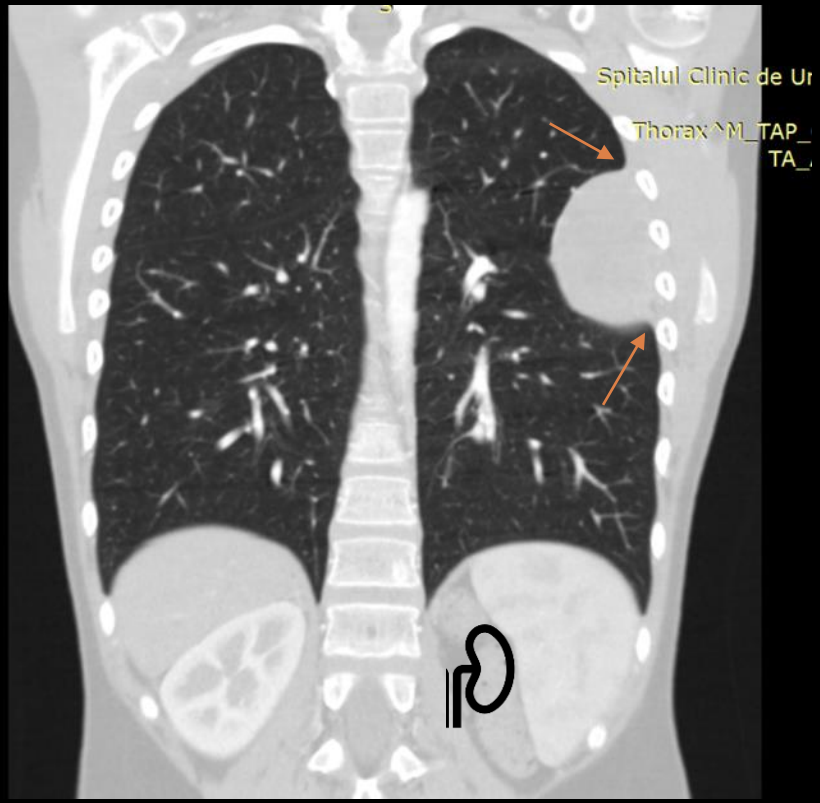
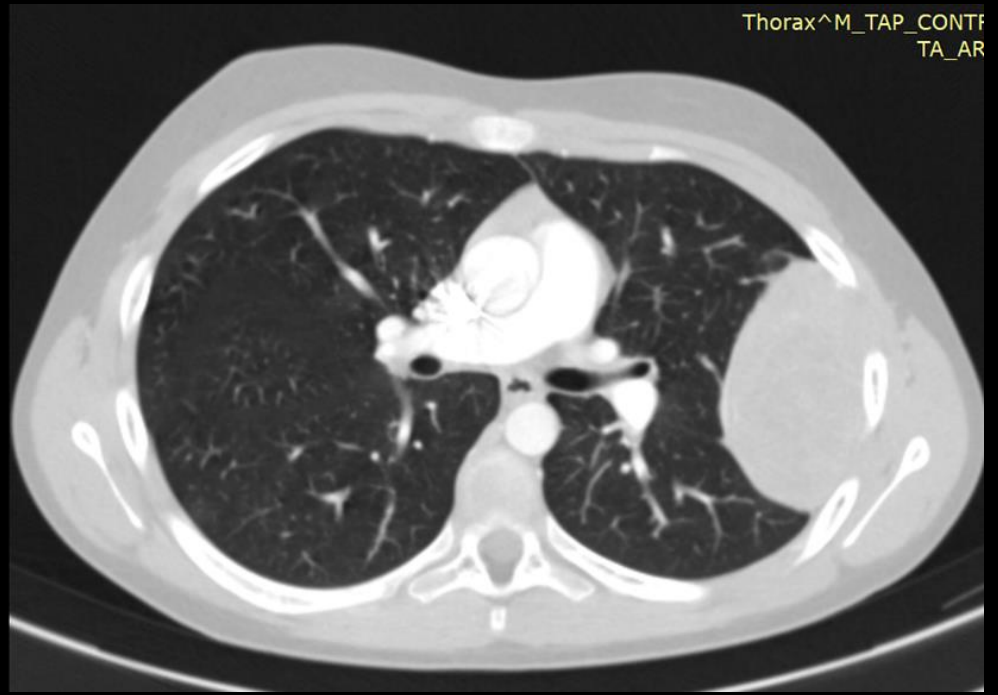
→Intermediate Risk
Diagnosis
Dec. 2010
Jun. 2011
ChT→ Surgery →ChT
Dec. 2010- June 2011
4w ChT (AV)
Total Nephrectomy
27w postOp ChT (AV)
No RT
➢ High Risk
Pulmonary Metastasis
May 2012
ChT
➢ 7C PoliChT
8.5y
Pleuro-Pulmonary Relapse
Feb.2021


Spitalul Clinic de Ur
Thorax^M_TAP_
TA_


Thorax^M_TAP_CONTR
TA_AR

March 2021- Metastasectomy

Descriere macroscopica:

Piesa de 10,5/6/4 cm reprezentata de o formatiune tumorala aparent incapsulata, de consistenta elastica, gri-alba cu arii violacei pe sectiune.

Descriere microscopica:

Materialul primit si examinat este reprezentat de o proliferare tumorala net delimitata de o pseudocapsula conjunctiva fina. Formatiunea tumorala este alcatuita in cea mai mare parte (85%) din celule de talie mica sau medie, fara limite celulare evidente, cu citoplasma redusa si nucleu mare, cu cromatina fin dispersata, fara nucleoli, dispusi suprapus, realizand mici grupuri sau trabecule separare de o stroma laxa, redusa cantitativ. Pleomorfismul nuclear este redus, iar mitozele numeroase, ajungand in unele zone la 15/10 HPF, majoritatea tipice. Printre acestea se observa rare structuri tubulare, unele cu secretie eozinofila in lumen, sau pseudorozete alcatuite din celule cu aspect epitelioid, poligonale, cu limite celulare slab vizibile, citoplasma in cantitate moderata si nuclei ovalari, palizi, cu nucleoli evidenti.

Stroma tumorala este reprezentata de tesut lax, in cantitate redusa, la nivelul caruia se observa celule cu aspect rabdoid, de talie mare, cu citoplasma eozinofila in cantitate moderata si nucleu excentric.

Intratumoral sunt prezente mici arii de necroza, redus infiltrat inflamator limfocitar dispus focal si arii de hemoragie.

Nu se identifica arii de anaplazie in sectiunile examinate.

Nu se oserva emboli tumorali limfatici (L0) sau venosi (V0) in sectiunile examinate.

Focal grupuri de celule tumorale blastemale sunt situate in afara pseudocapsulei formatiunii tumorale.

Marginile de rezectie sunt libere de leziune, dar trec focal la 1 mm de celulele tumorale.

Imunohistochimic, celulele tumorale sunt pozitive in coloratiile pentru PAX8, CKAE1/AE3, CD56. Coloratia pentru Vimentina este pozitiva pe celulele stromale si pe o parte din celulele tumorale. Coloratiile imunohistochimice pentru CD99, Desmina, Sinaptofizina si WT1 sunt negative.

Diagnostic histopatologic:

Aspectul histopatologic, corelat cu testele imunohistochimice efectuate si cu datele clinice pledeaza pentru o recidiva a nefroblastomului (cu lipsa aberanta a expresiei pentru WT1) cunoscut si tratat la acest pacient.

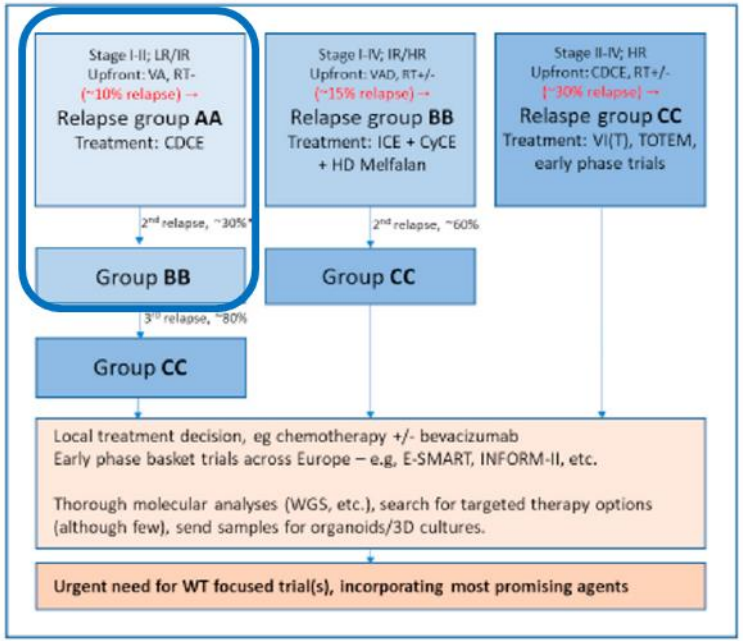
- ❑ No anaplasia
- ❑ L0, V0
- ❑ R0, 1mm margin
- ❑ WT1 (IHC neg)

https://en.wikipedia.org/wiki/Wilms%27_tumor

Q4: Further treatment?

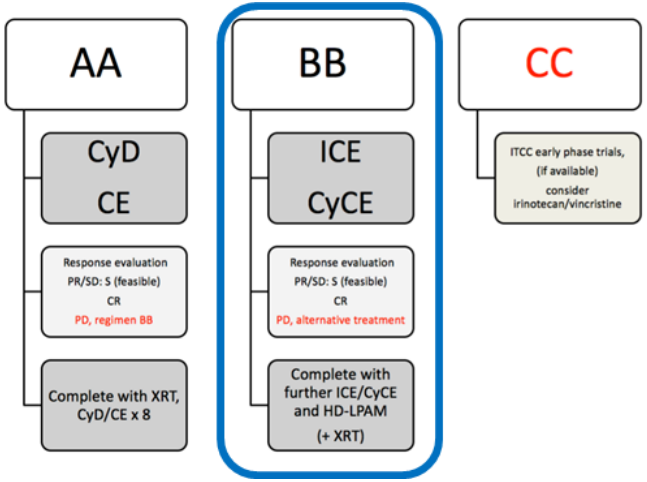
a) Chemotherapy only
b) Chemotherapy+ Local RT
c) Chemotherapy + Whole Lung RT
d) Local RT only
e) Whole Lung RT only

Further treatment

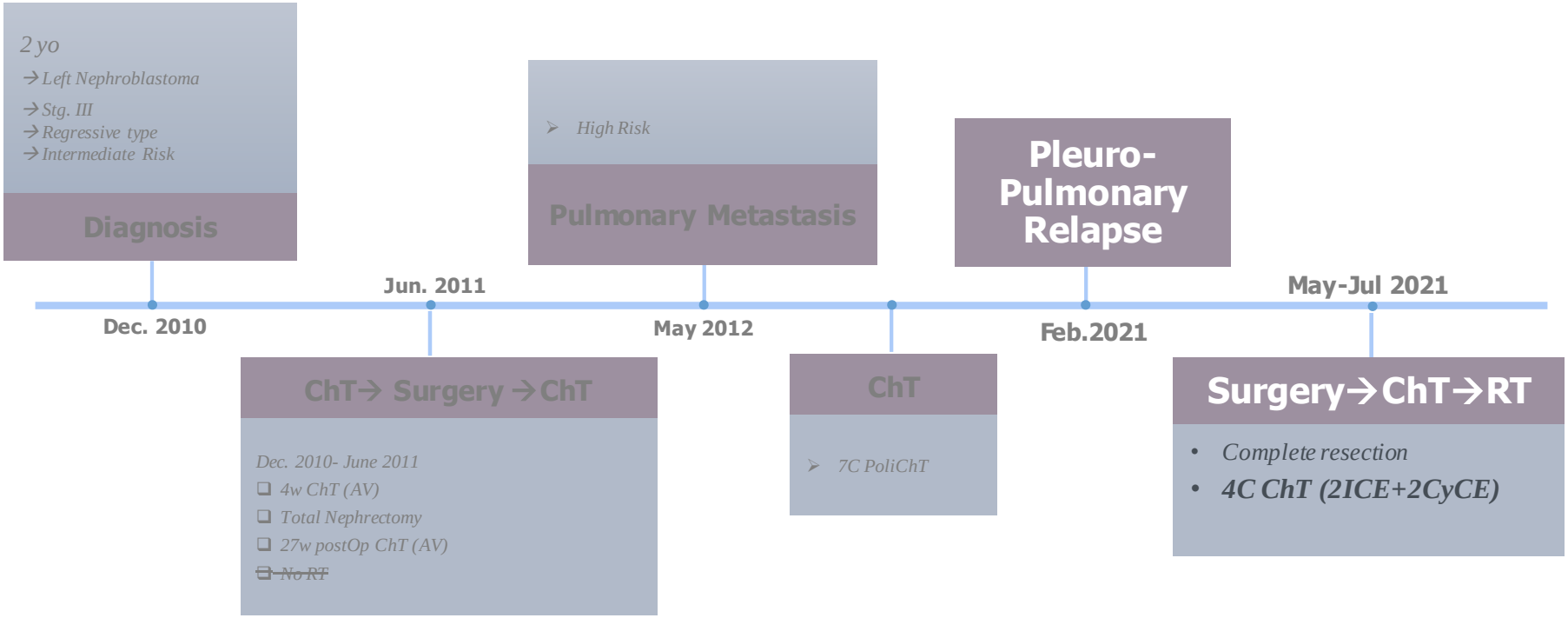


Group BB: Patients **without** initial diffuse anaplasia, or blastemal-type after pre-operative chemotherapy, treated initially with ≥3 chemotherapy drugs with or without radiation. Patients with second and subsequent relapses may be entered if prior therapy was according to group AA, in the absence of alternative treatment solutions by the responsible treating physician.

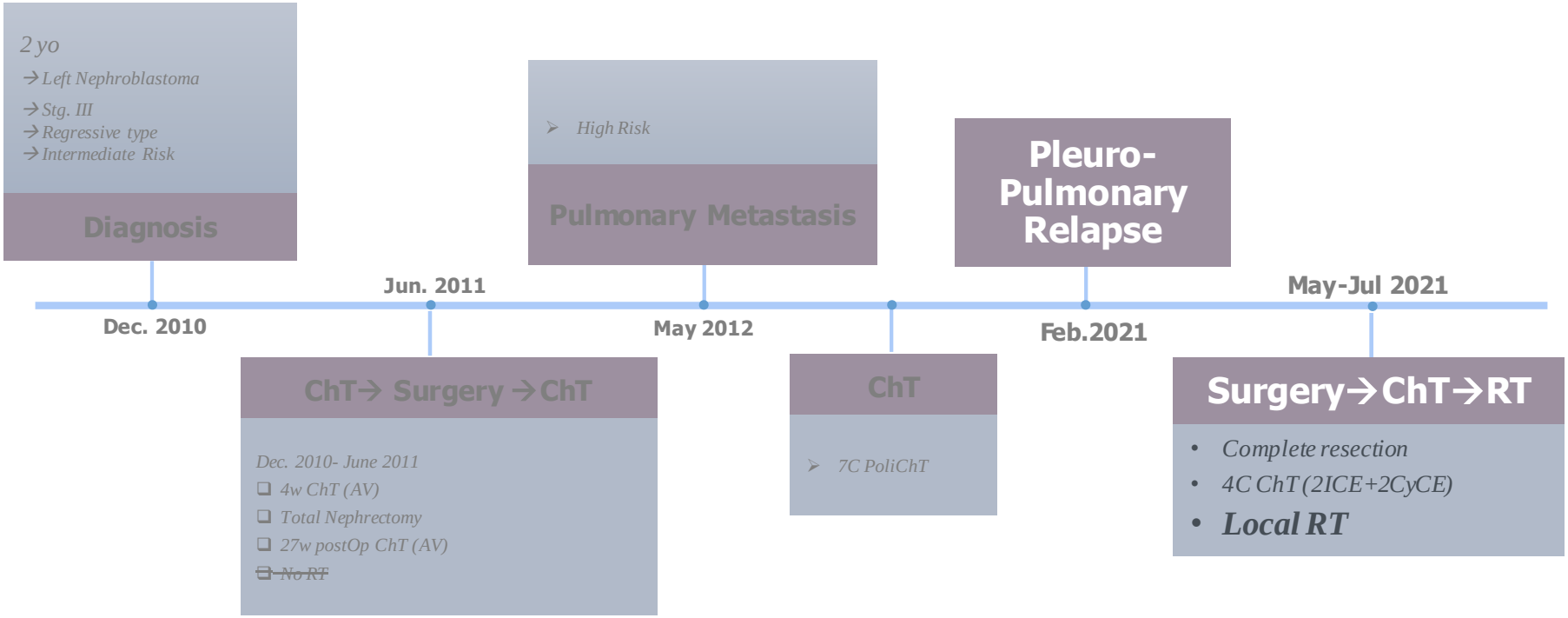
This group, accounting for 45-50% of the children with WT who relapse, is expected to have survival rates in the 40-50% range



Timeline


2 yo
→Left Nephroblastoma
→Stg. III
→Regressive type
→Intermediate Risk
Diagnosis
Dec. 2010
Jun. 2011
ChT→ Surgery →ChT
Dec. 2010- June 2011
4w ChT (AV)
Total Nephrectomy
27w postOp ChT (AV)
No RT
➢ High Risk
Pulmonary Metastasis
May 2012
ChT
➢ 7C PoliChT
Pleuro-Pulmonary Relapse
Feb.2021
May-Jul 2021
Surgery→ChT→RT
• Complete resection
• 4C ChT (2ICE+2CyCE)

Timeline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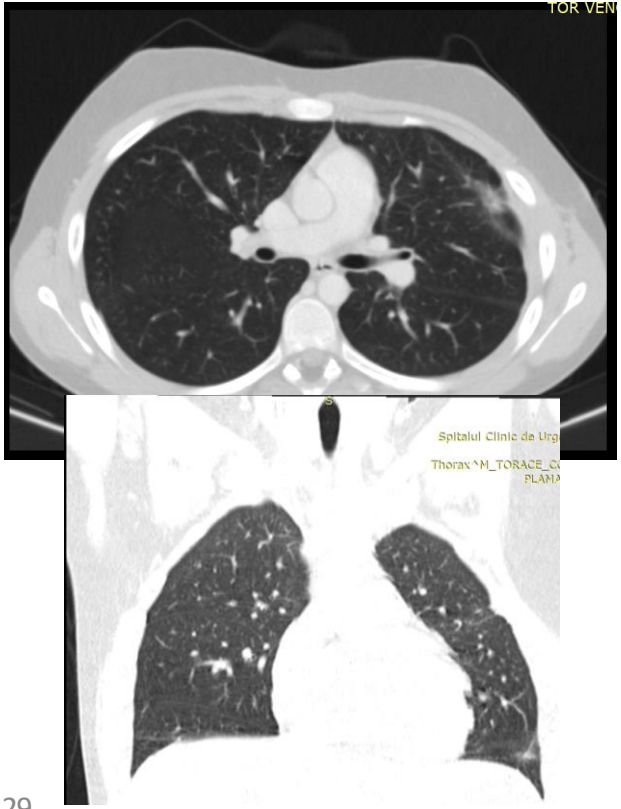
Pulmonary Metastasis
May 2012
ChT
➢ 7C PoliChT
Pleuro-Pulmonary Relapse
Feb.2021
May-Jul 2021
Surgery→ChT→RT
Complete resection
4C ChT (2ICE+2CyCE)
Local RT

Radiotherapy



- Target volume
  - **CTV=Tumor bed**
  - **PTV=CTV+1cm**

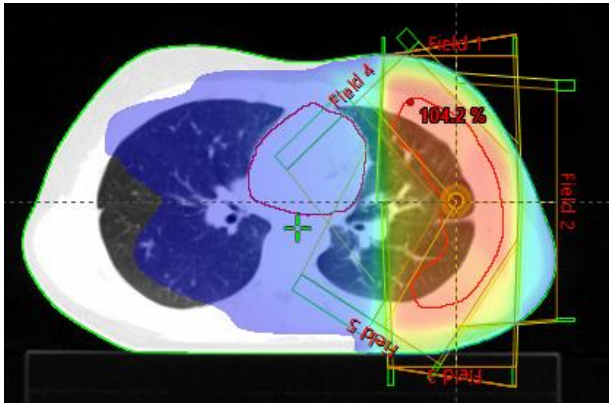
- Dose prescription
  - 25.2 Gy/ 14 fr (1.8Gy/fr)

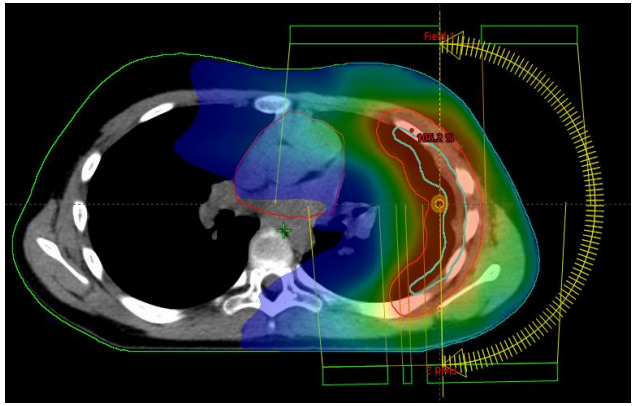
Dose and fractionation SIOP 2016

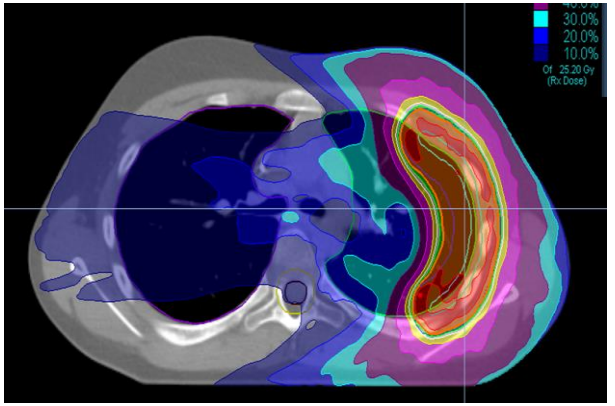
- The total dose is 12 Gy (intermediate risk) and 15 Gy (high risk) for both lungs.
- The dose per fraction is 1.5 Gy (with homogeneity correction), delivered within 8-10 fractions.

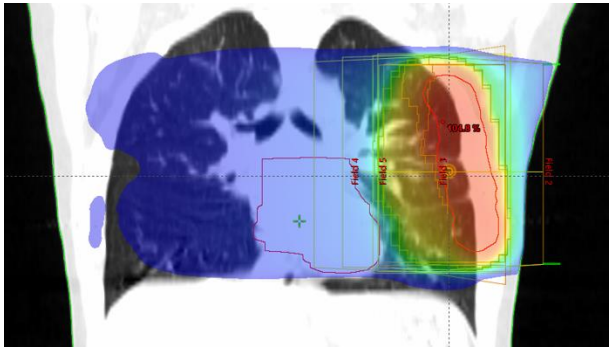
A boost of 10-13 Gy (intermediate risk histology) and 15-20 Gy (high risk histology) should be considered for areas of macroscopic residual disease after surgery using highly conformal radiation techniques (SBRT), if possible and normal tissue dose constraints can be respected.

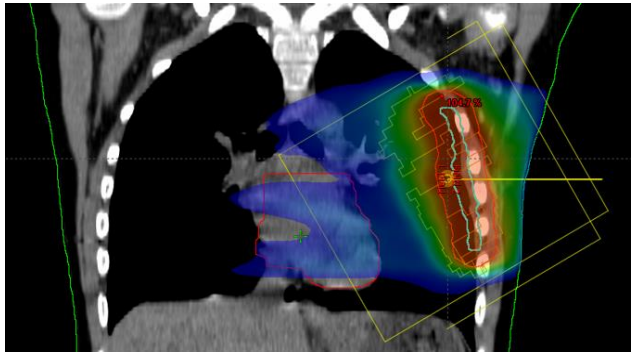
3DCRT VMAT HT

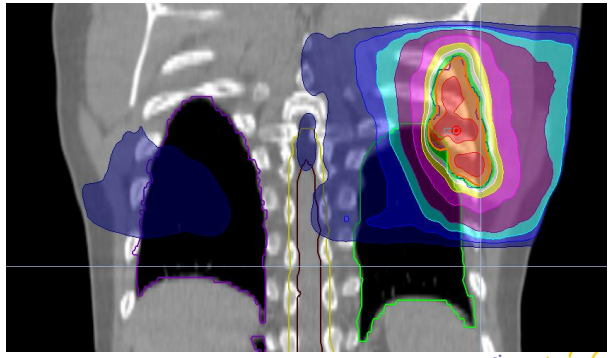




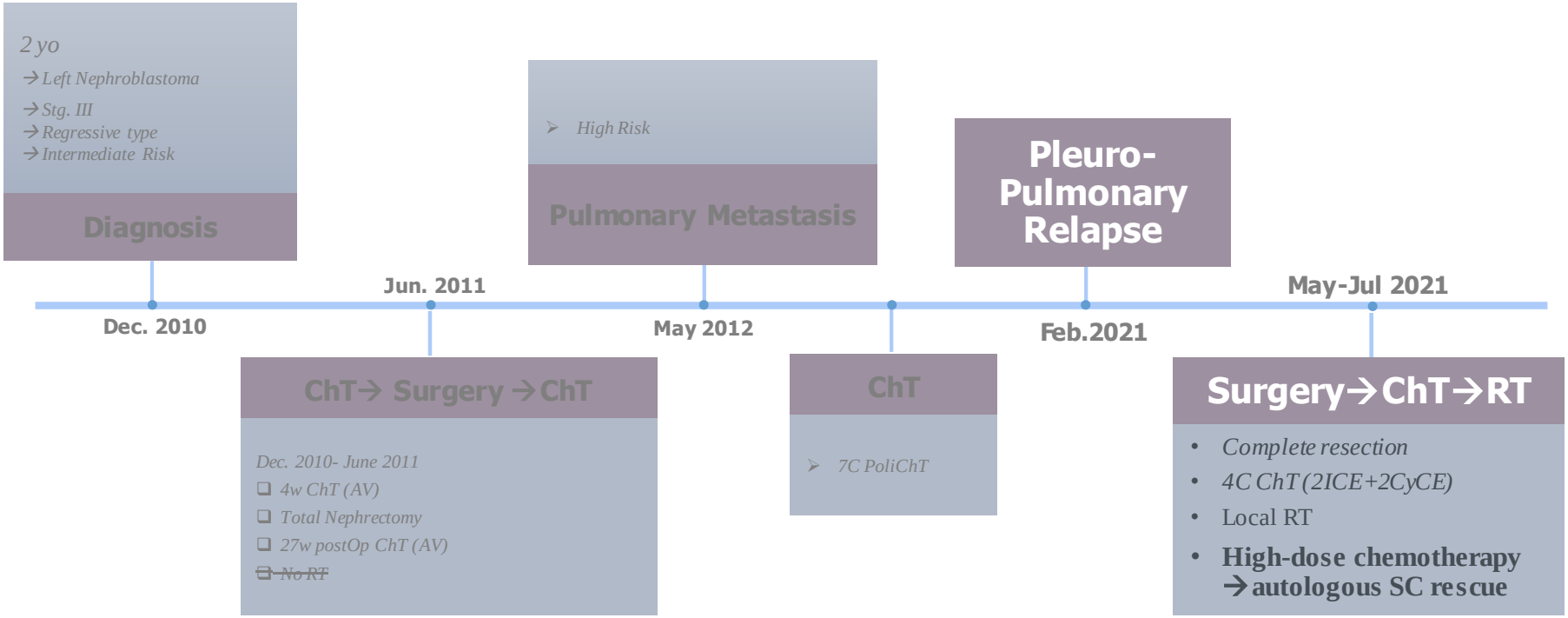








Timeline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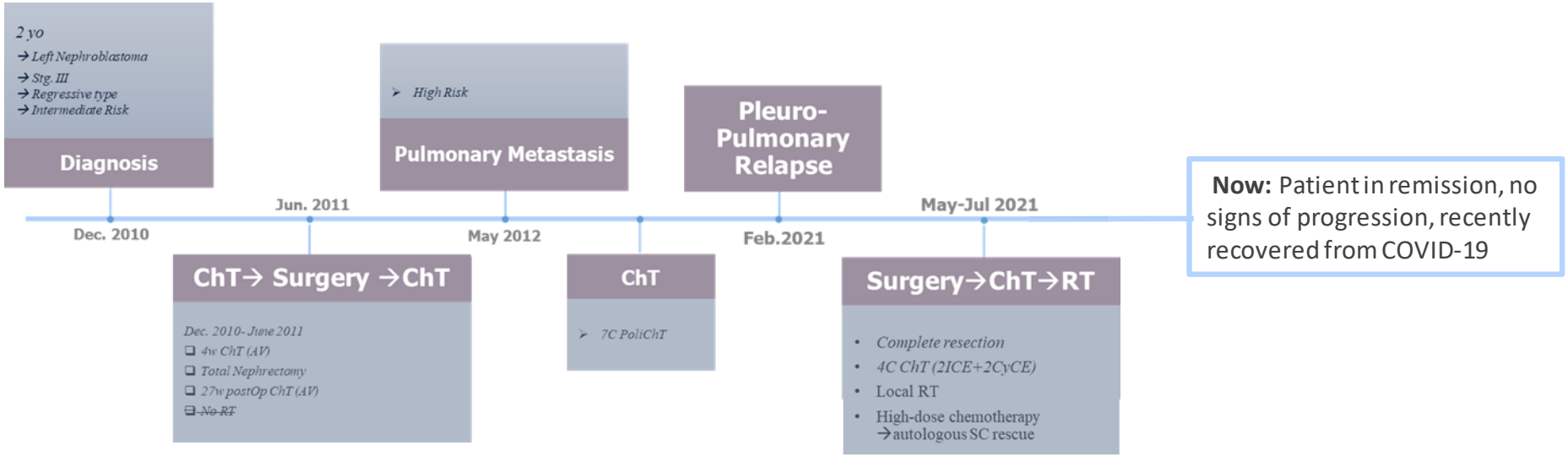
→Intermediate Risk
Diagnosis
Dec. 2010
Jun. 2011
ChT→ Surgery →ChT
Dec. 2010- June 2011
4w ChT (AV)
Total Nephrectomy
27w postOp ChT (AV)
No RT
➢ High Risk
Pulmonary Metastasis
May 2012
ChT
➢ 7C PoliChT
Pleuro-Pulmonary Relapse
Feb.2021
May-Jul 2021
Surgery→ChT→RT
Complete resection
4C ChT (2ICE+2CyCE)
Local RT
High-dose chemotherapy →autologous SC rescue

Timeline


2 yo
→ Left Nephroblastoma
→ Stg. III
→ Regressive type
→ Intermediate Risk
Diagnosis
Dec. 2010
ChT→ Surgery →ChT
Dec. 2010- June 2011
4w ChT (AV)
Total Nephrectomy
27w postOp ChT (AV)
No RT
Jun. 2011
High Risk
Pulmonary Metastasis
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Feb.2021
Surgery→ChT→RT
Complete resection
4C ChT (2ICE+2CyCE)
Local RT
High-dose chemotherapy →autologous SC rescue
May-Jul 2021
Now: Patient in remission, no signs of progression, recently recovered from COVID-19

Discussions

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

General challenges

- Therapeutic decision- not discussed in a Multidisciplinary Team meeting
- No National Guidelines/Consensus to follow
- Patient records/imaging- hard to obtain/no national cancer registry
- No access to clinical trials

Primary tumor

- ChT as per experimental arm (*SIOP WT 2001*)
- ~~No flank RT~~
  - *Infrastructure ok → Poor interdisciplinary communication ?*

First relapse

- Early- 9 months
- ~~No Surgery, No RT~~ / just **ChT** (as per another trial protocol)

Second relapse

- Late- almost 9 years
- Same Lung (left) as the first metastasis- **Pleural**
- Radiotherapy-no specific guidelines for this scenario
  - *Would WLI have been a better option?*

☺ *Relatively good outcome – Favorable tumor biology ?*

Brief Report

Wilms Tumor with Pleural Metastasis

Global Pediatric Health
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Case Reports › Nucl Med Rev Cent East Eur. 2011;14(1):33-5. doi: 10.5603/nmr.2011.0007.

Potential role of PET-CT in chemotherapy efficacy assessment and recurrence diagnosis in a patient with a Wilms' tumour

Piotr Piwkowski [1], Andrzej Kołodziejczyk, Adam Macioszek, Katarzyna Połczyńska, Jacek Zebrowski

Affiliations + expand
PMID: 21751170 DOI: 10.5603/nmr.2011.0007
Free article

Case Reports › Diagn Cytopathol. 2002 Feb;26(2):99-103. doi: 10.1002/dc.10048.

Wilms' tumor in adults: aspiration cytology and cytogenetics

Peng Li [1], Mary Ann Perle, John V Scholes, Grace C H Yang

Affiliations + expand
PMID: 11813327 DOI: 10.1002/dc.10048

Abstract

The fine-needle aspiration cytologic findings of Wilms' tumor occurring in a 20-yr-old female patient and a 35-yr-old male patient showing blastemal, spindled sarcomatous and rare epithelial components are reported. The male patient had the typical presentation of renal mass with metastasis to lung and pleura, whereas the female patient had an unusual presentation with the tumor originated from the subcapsular nephrogenic zone of the kidney, extending into the liver without invasion into the renal cortex. Cytogenetic analysis of this case identified: 90, XXXX, +2x3-4, -5, -15,

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