ESPR
European Society of Paediatric Radiology

56th Annual Meeting &
42nd Post Graduate Course

The ongoing UMBRELLA / RANDOMET studies for kidney tumors

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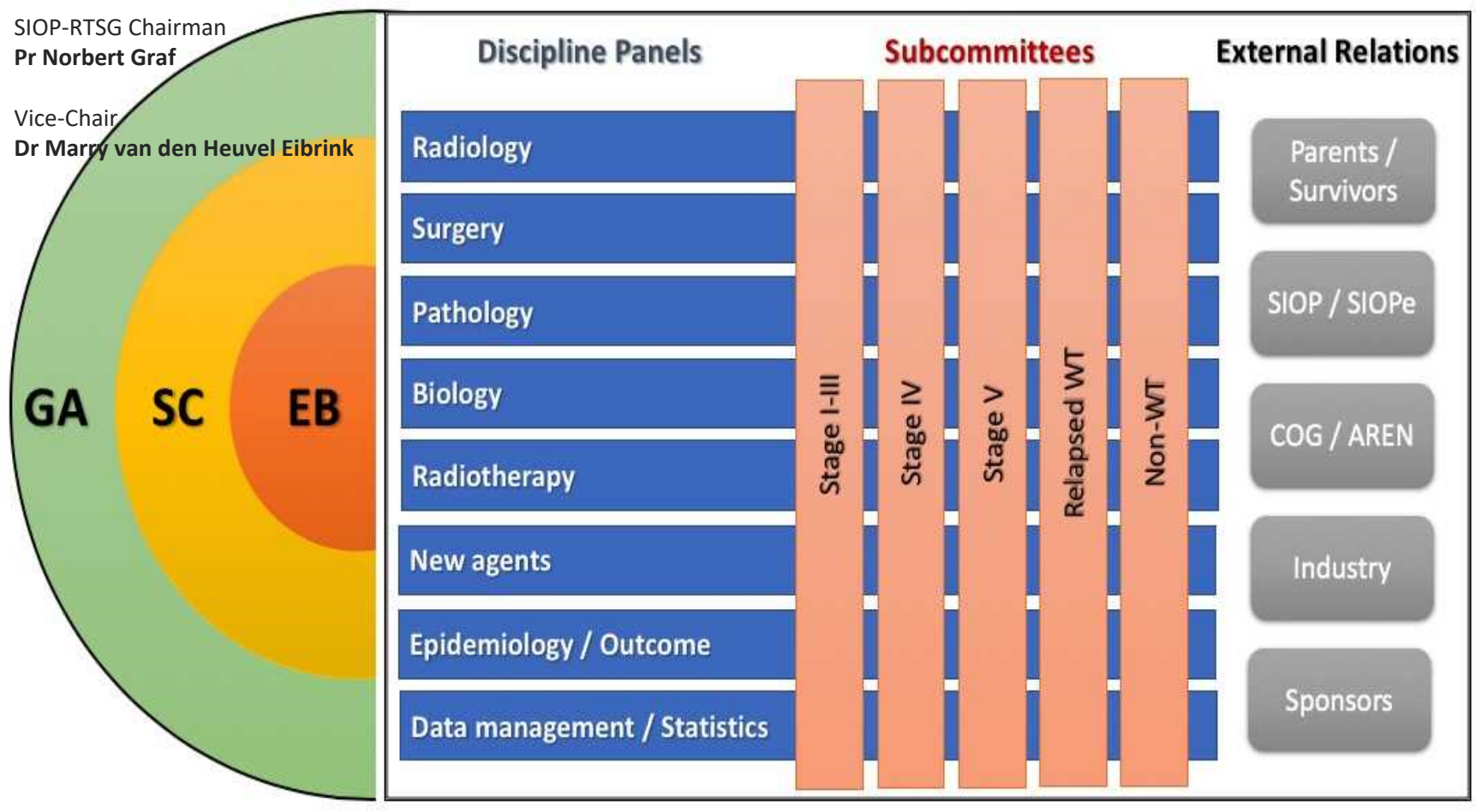
The SIOP Renal Tumor Study Group

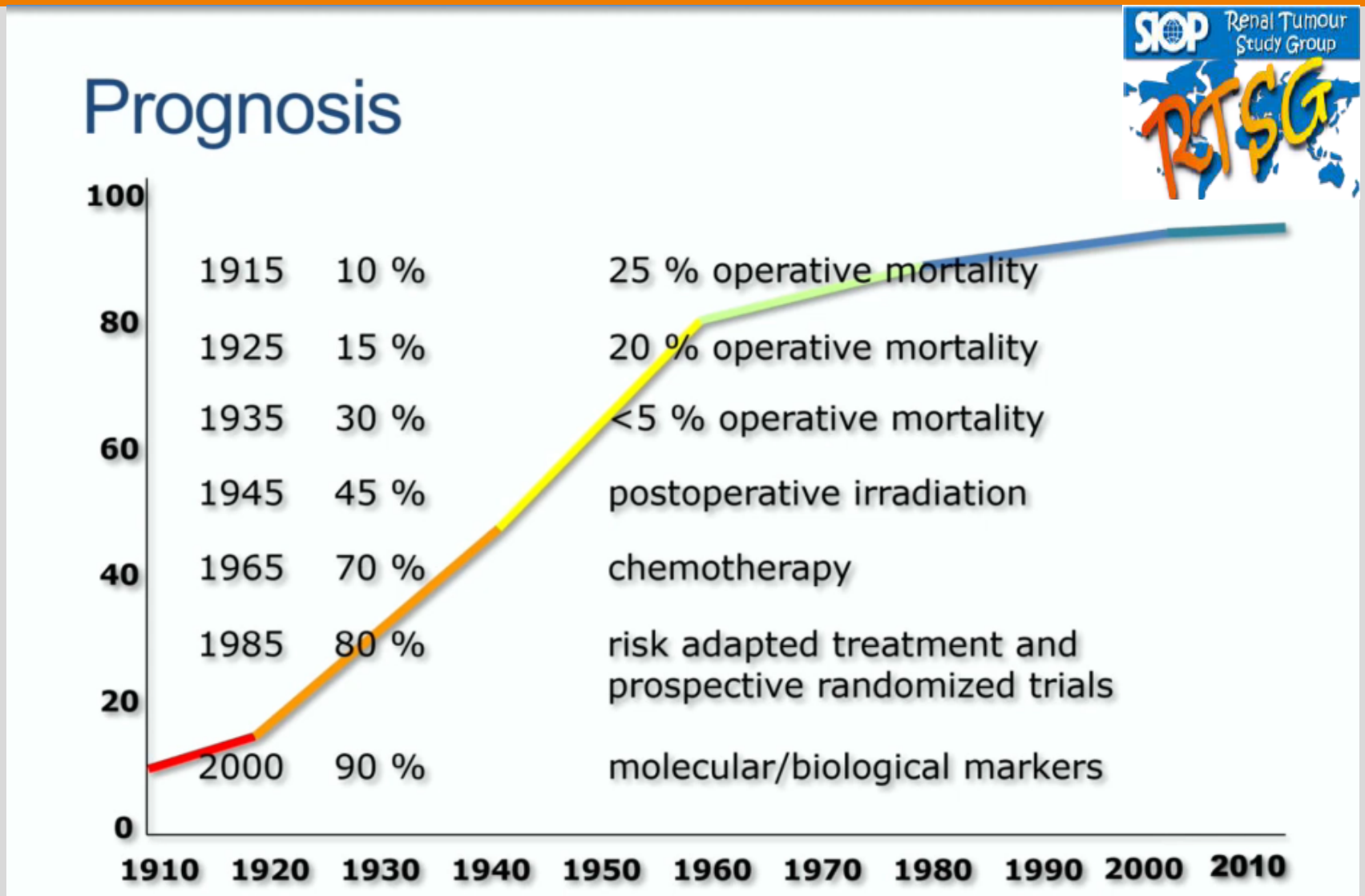


SIOP Renal Tumour Study Group RTSG

Radiology Panel

J-P Schenk (chair)
HJ Brisse (co-chair)

The Wilms' tumor success story



SIOP Wilms tumors trials & studies

Chemotherapy descalation

• SIOP 1	1971 – 1974	338	Patients
• SIOP 2	1974 – 1976	138	
• SIOP 5	1977 – 1979	397	
• SIOP 6	1980 – 1987	1095	
• SIOP 9	1987 – 1991	852	
• SIOP 93-01	1993 – 2001	2162	
• SIOP 2001	2001 – 2015	5728	
		10710	

- *28 countries*
- *261 centres*

SIOP 2001 - Outcome

Total Nr. at Risk(T_0)	Events(2y) Survival(2y)	Stage I	Stage II	Stage III	Stage IV	All stages
Low Risk		75 75	3 (95%)	6 6	0 (100%)	16 16	0 (100%)	49 48	3 (92%)	146 145	6 (95%)
Intermediate Risk		927 912	58 (93%)	432 424	34 (90%)	361 356	41 (85%)	262 257	55 (73%)	1982 1949	188 (87%)
High Risk		104 98	11 (85%)	71 70	13 (76%)	98 92	23 (67%)	51 49	28 (36%)	324 309	75 (69%)
All		1106 1085	72 (91%)	509 500	47 (88%)	475 464	64 (82%)	362 354	86 (70%)	2452 2403	269 (85%)

SIOP-RTSG, Interim Report

Umbrella SIOP – RTSG 2016

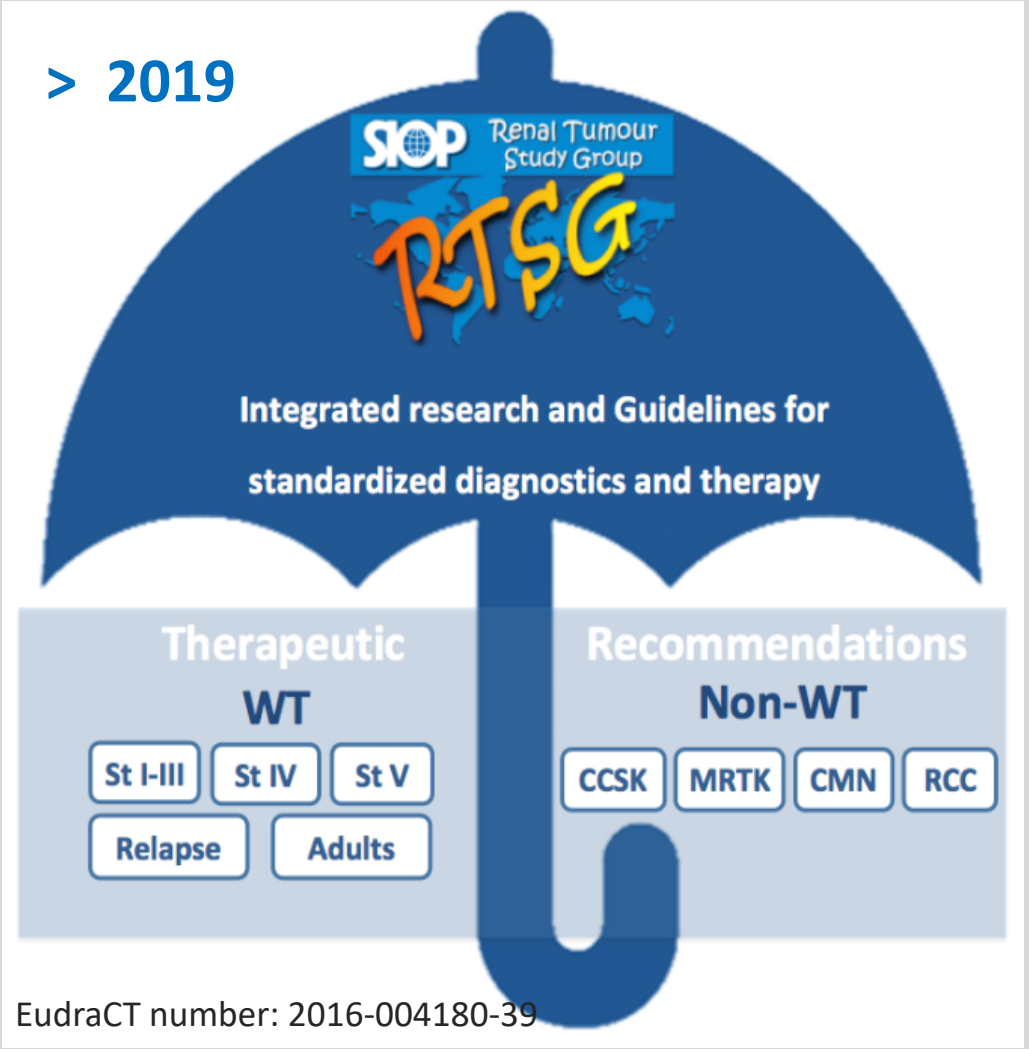
Chairs UMBRELLA:
N. Graf
& M.M. van den Heuvel-Eibrink

Central Datamanager:
P. Roy & R. Koolma

Projectmanagers:
C. van Overbeek & S. van der Kroef

Statistics:
H. van Tinteren

Contact:
SIOP-UMBRELLA-dm@prinsesmaximacentrum.nl



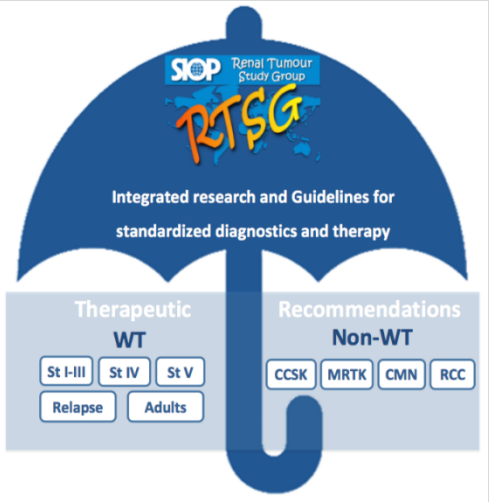
EudraCT number: 2016-004180-39

Umbrella SIOP-RTSG – Primary aims

- ***Not*** **a clinical trial**
- **Wilms Tumors & non-WT**
- **Standardized treatment guidelines, based on**
  - SIOP 2001
  - UK Import 2013
- **Database to define prognostic factors/biomarkers**
  - Histopathology: *blastemal* subtype definition
  - Genetics
    - 1p & 16q LOH, 1q gain
    - WT1, CTNNB1, AMER1, TP53, MYCN, FBXW7, GPC3, MLLT1, DIS3L2, DICER1, DROSHA, DGCR8, SIX1 and SIX2
  - Imaging

➢ **Basis for future SIOP trials**: better stratification / personalized treatment

Umbrella SIOP-RTSG – Secondary aims

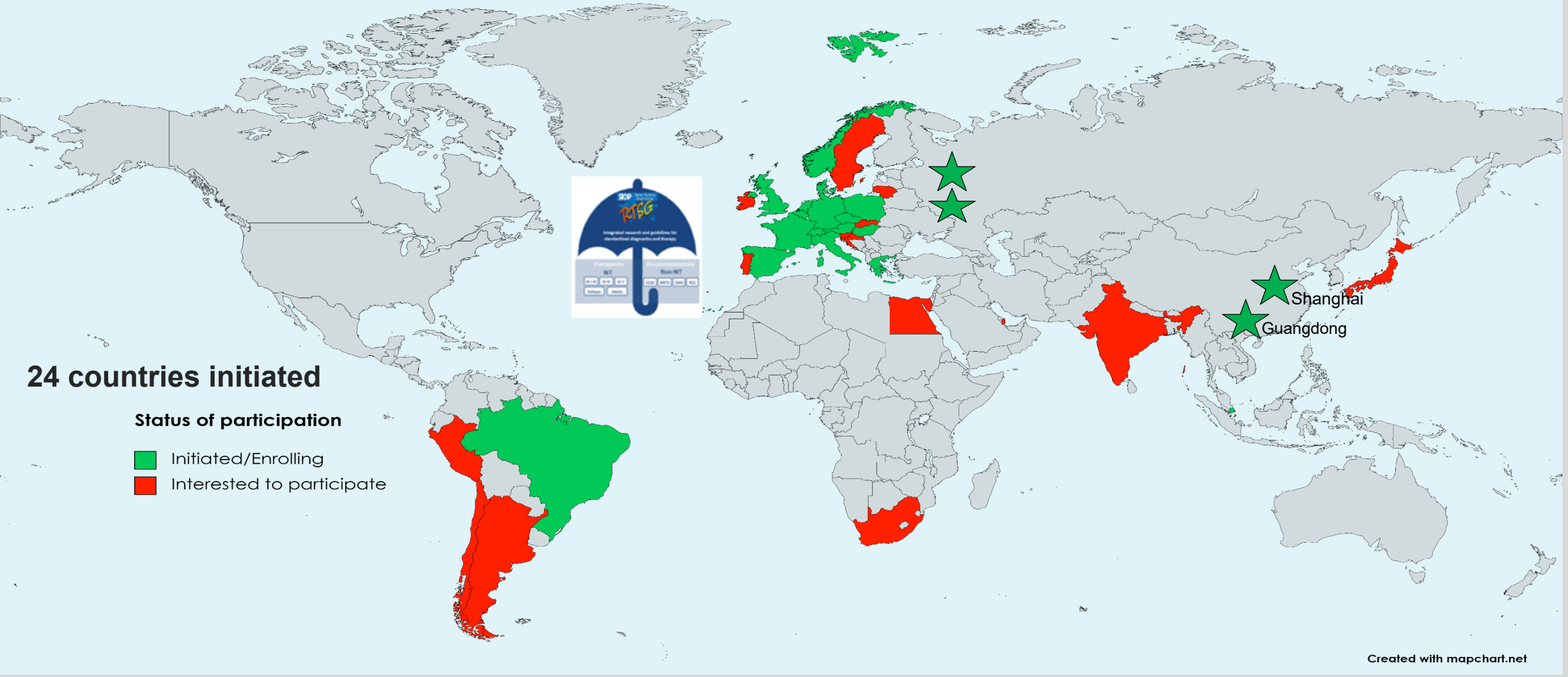


- **To increase quality control**
  - Pathology central review
  - Radiology central review
  - Surgical review process / Nephron-sparing surgery

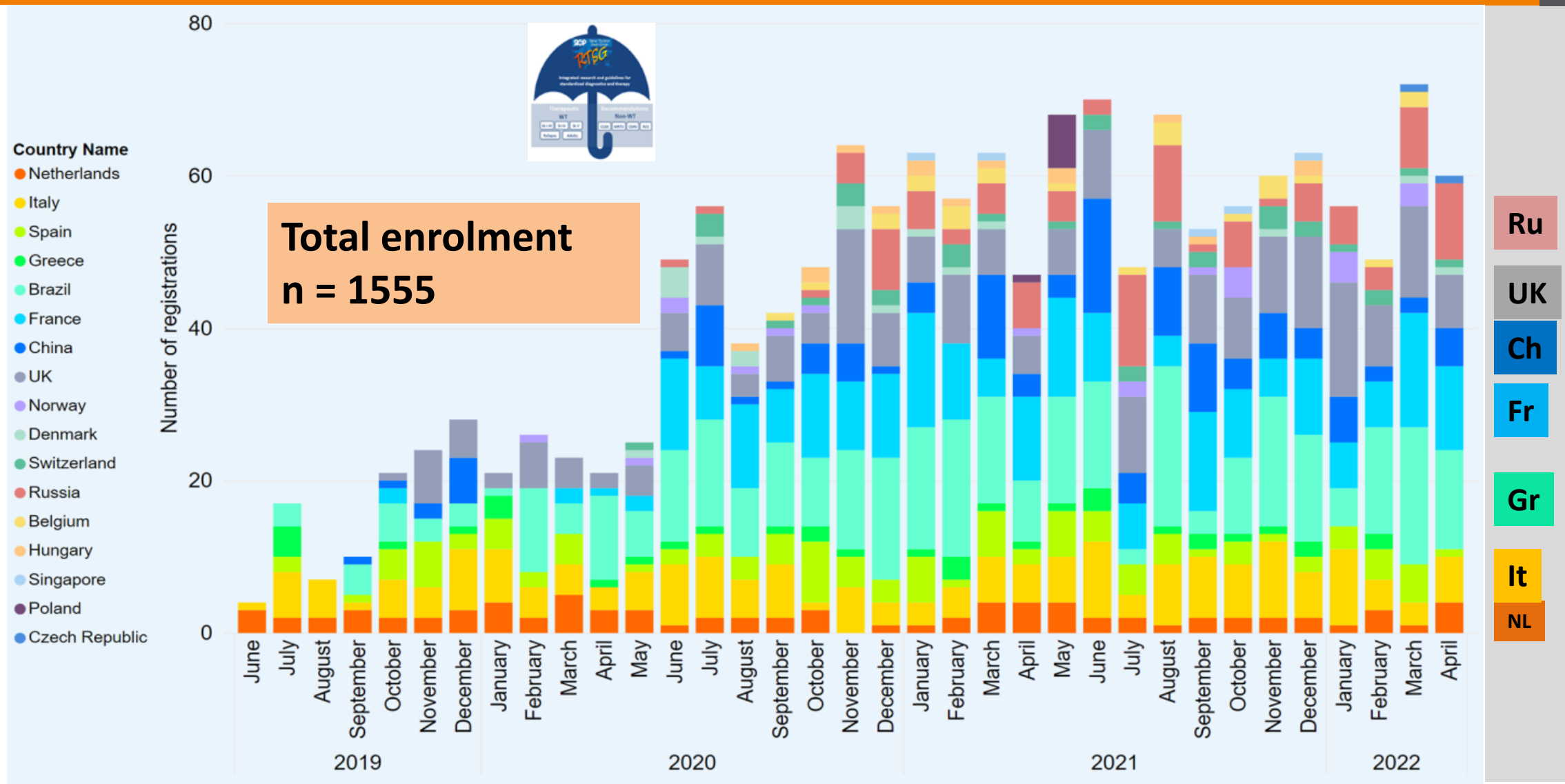
- **To improve infrastructures**
  - International central database: e-CRF (ALEA®)
  - Data exchange / storing (pathology, imaging): national level
  - Biological samples collection

- **To foster international collaborations** / networking

Umbrella – SIOP – RTSG 2016



Umbrella Enrolment (as of April 2022)



SIOP Current treatment: Localized unilateral WT

> Neoadj chemo
AV1 (4 weeks)

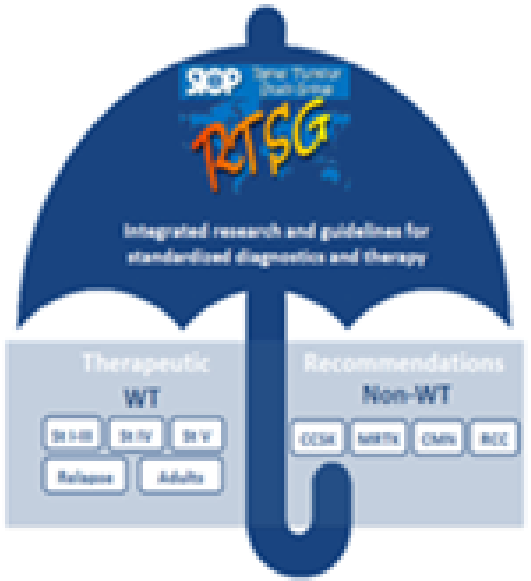
		Tumour volume after preoperative chemotherapy	Stage I 	Stage II	Stage III
Low Risk (only CN)		All	No further treatment	AV2 (27 weeks)	AV2
Intermediate Risk		≤ 500 ml	AV1 (4 weeks)	AV2	AV2 + RT
Intermediate Risk* (Except stromal & epithelial)		> 500 ml	AV1	AVD	AVD + RT
High Risk	**Blastemal Type**	All	AVD (27 weeks)	HR-1 (34 weeks Cyclo-dox VP16-CarboP)	HR-1 + RT
	Diffuse Anaplasia	All	AVD	HR-1 + flank RT	HR-1 + RT

Central Radiology Review

7.1.2 Central radiology review

Each national centre needs to determine where central radiology review will be done in order to analyse the requested imaging studies in a standardized way to take part in the SIOP 2016 UMBRELLA protocol. Independent expert radiologists should do the second view. National/Regional Chairs for Central Radiology Review are the following:

AIEP (Italy)	Carlo Morosi
Austria	Karoly Lakatos
Belgium	Luc Breysem
CCLG (UK)	Oystein Olsen
DCOG (The Netherlands)	AS Littooij
GBTR (Brazil)	Henrique Lederman
GPOH (Germany)	Jens-Peter Schenk
NOPHO (Scandinavian countries)	Lena Gordon (Sweden)
Poland	Dorota Sosnowska
SEHOP (Spain)	Ana Coma
SFCE (France)	Hervé Brisse
Switzerland	Christian Kellenberger
SIOP (all other countries)	NN

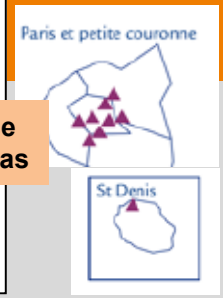


Central Radiology Review

Ile de France /Ile de la Réunion (CANPEDIF)

- CLCC Institut Gustave Roussy - Villejuif - **Coordonnateur**
- Hôpital Armand Trousseau - Paris
- Hôpital Robert Debré - Paris
- Hôpital Saint-Louis - Paris
- Institut Curie - Paris
- Fondation Rotschild - Paris
- Hôpital du Kremlin Bicêtre - Paris
- Hôpital Necker - Paris
- Centre Hospitalier Départemental Félix Guyon - Réunion

H Brisse
N Nicolas



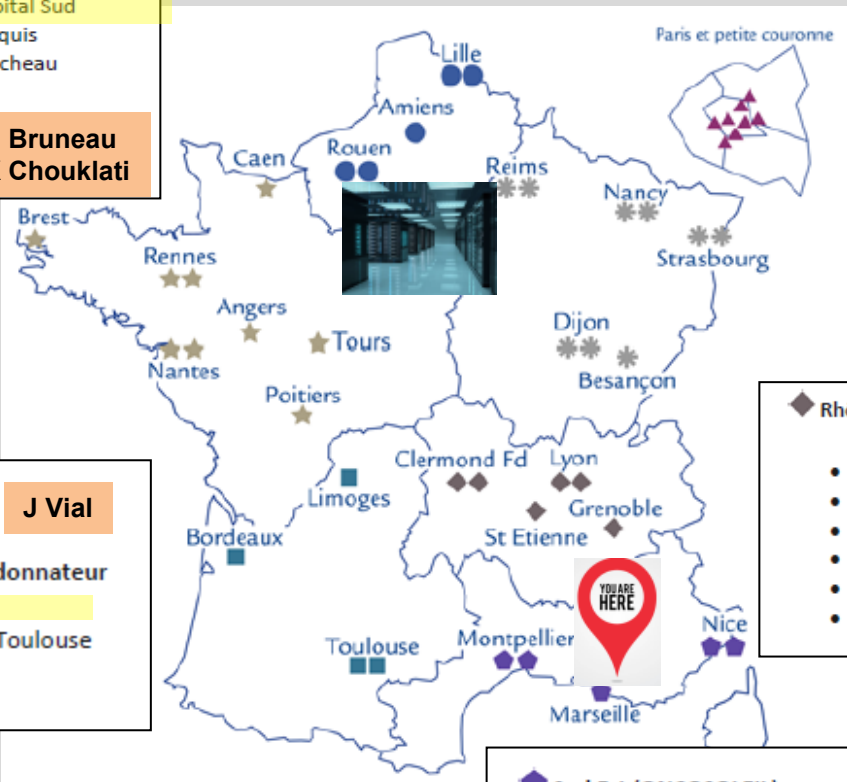
Nord Ouest (RIOP-NO) — **C Fayard**

- CLCC Oscar Lambret - Lille -Coordination alternée
- CHU Amiens -Coordination alternée
- CHU de Rouen -Coordination alternée
- CHU de Lille
- CLCC Henri Becquerel – Roue

Grand Ouest (GOCE)

- CHU d'Angers -**Coordinateur**
- CHU Nantes -
- CHU de Caen
- CHU Brest
- CHU de Tours
- CHU Rennes - Hôpital Sud
- CLCC Eugène Marquis
- CLCC René Gauducheau
- CHU de Poitiers

B Bruneau
K Chouklati



Grand Est (GE-HOPE) — **F Gabor**

- CHU de Nancy -**Coordonnateur**
- CLCC Alexis Vautrin - Nancy
- CHU de Besançon
- CHU de Dijon
- CLCC GF Leclerc-Dijon
- HUS Strasbourg
- CLCC Paul Strauss - Strasbourg
- CHU Reims
- CLCC Jean Godinot – Reims

Rhône-Alpes/Auvergne (Auracle)

- CLCC Léon Bérard - Lyon -**Coordonnateur**
- Hospices civils de Lyon
- CHU de Clermont-Ferrand
- CLCC Jean Perrin - Clermont Ferrand
- CHU de Grenoble
- CHU de Saint Etienne

M Lemery
JM Garcier

Sud Ouest (ISOCELE) — **J Vial**

- CHU de Bordeaux -**Coordonnateur**
- CHU de Toulouse
- CLCC Claudius Regaud - Toulouse
- CHU de Limoges

Sud Est (ONCOSOLEIL) — **Ph Petit**, **A Aschéro**

- AP-HM La Timone -**Coordonnateur**
- CHU de Montpellier
- GCS CHU de Nice - Fondation Lenval
- CLCC Lacassagne Nice
- Institut régional du cancer de Montpellier

sfipp
SOCIÉTÉ FRANCOPHONE D'IMAGERIE PÉDIATRIQUE & PRÉNATALE

~ 100 patients/year
7 regions / SFCE
1-2 Referent Rx/region

Secured REDIOP exchange network
National DICOM database (GDPR)

Central Radiology Review: Time points

- **At diagnosis**
  - Wilms vs Non-Wilms / indications for primary surgery or biopsy ?
  - Presumed WT :
    - Unilateral or bilateral disease/nephroblastomatosis ?
    - Locoregional extension ? (Veins, LN, peritoneum)
    - Metastases ? Lungs +++, liver

- **Before renal surgery**
  - Local residual disease / tumor volume
  - Metastatic response

- **Week 9 of postoperative chemotherapy** (for non-CR Stage IV)
  - Metastatic response

- **End of treatment** (Stage IV)
- **Recurrences**

SIOP-RTSG Guidelines for CNB of kidney tumors

(genetic predisposition excluded)

	Biopsy NOT recommended **Features typical of WT** ALL criteria required	**Biopsy NOT recommended** if ANY of these criteria met	**Biopsy recommended** **if ANY of these criteria met**	**Indication to be discussed in TBM if ANY of these criteria**
Clinical criteria	**6m ≤ Age < 7y** *No* infectious syndrome	**Age <3m** (upfront surgery)	**Age ≥ 10 y** 7 ≤ Age <10 y + *vol* < 200mL	3 m ≤ Age < 6 m Infectious syndrome Urinary tract infection
Radiological criteria	**Obvious renal origin** **Unilateral tumor** **Tumor volume > 80 mL** **Solid or mixed** (solid and cystic) tumor No calcification Metastases absent or lung mets *and* age ≥ 2y	**Totally cystic** tumor (primary surgery) **Bilateral** kidney tumors or Nephroblastomatosis *and* age <7 y (presumptive chemotherapy)	**Uncertain renal origin** **Atypical metastases** for WT: - Bones - CNS - Lungs *and* age < 2y	Intra-tumor calcifications Tumor volume < 80 mL Major necrotic adenopathy Bilateral tumors and age > 7 y
Biological criteria	Normal urinary catecholamines Normal serum calcium LDH < 4 N		Elevated urinary **catecholamines** **Hypercalcemia** *and* age <4 y	**LDH > 4 N**

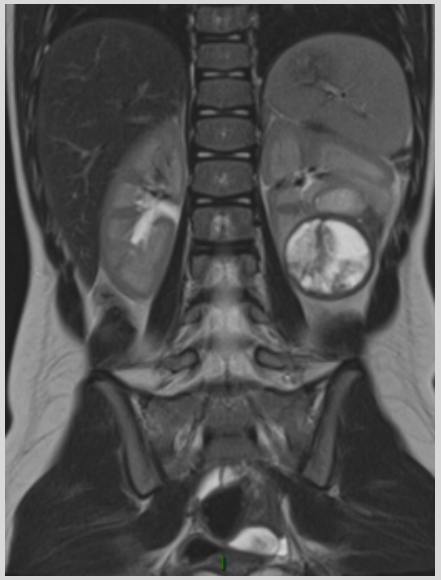
Primary Surgery

Neoadj. Chemo

Biopsy

Jackson TJ, Brisse HJ, Pritchard-Jones K, Nakata K, Morosi C, Oue T, Irtan S, Vujanic G, van den Heuvel-Eibrink MM, Graf N, Chowdhury T; SIOP RTSG Biopsy Working Group. How we approach paediatric renal tumour core needle biopsy in the setting of preoperative chemotherapy. **Pediatr Blood Cancer. 2022**

Keypoints for Radiologists: primary tumor

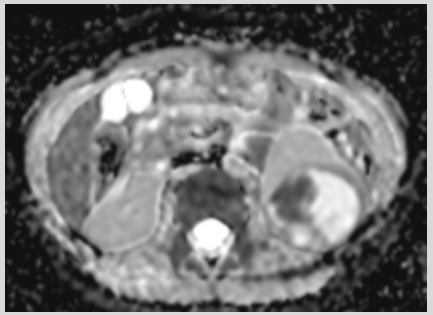


- **Technical issues**
  - **Assess the *whole* abdominal cavity**

  - **US** as first line (at diagnosis and day 15 mid-course of neoadjuvant chemo)
    - High frequency (> 10 MHz) probes (contralateral kidney / NRs)
    - Check the veins (RV, IVC): B-mode + doppler

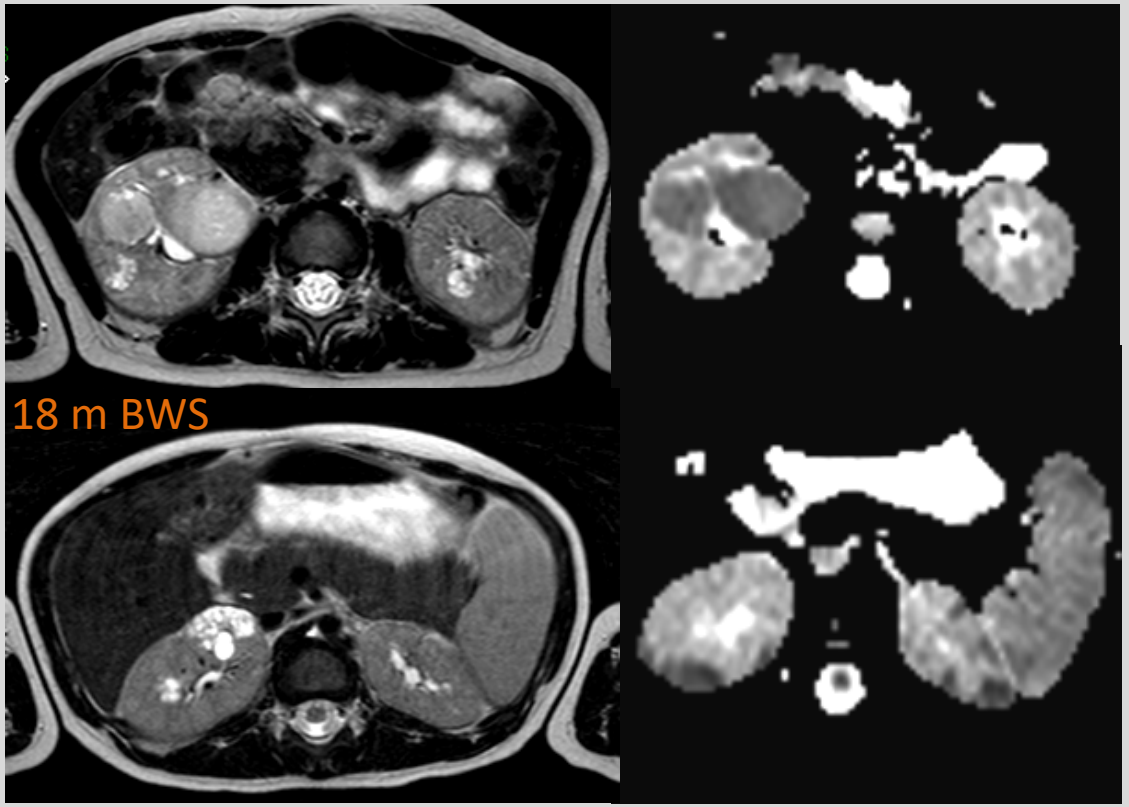
  - **MRI or CT is mandatory** (at diagnosis and before surgery)
    - **MRI should always be prefered**
      - For all patients, and especially for very young with bilateral/nephroblastomatosis
      - 2D axial & coronal planes or 3D T1 & **T2**, SW ≤ 4 mm and DWI ++
      - Gd-enhanced T1 optional

    - **CT** if MRI not available/feasable
      - Dose adaptation: neither adults protocol *nor ultra-low dose* !
      - Always with iv iodine contrast : one arterio-portal phase sequence is enough !



Keypoints for Radiologists: primary tumor

- **Reporting key points**



- ✓ Uni/bilateral disease
- ✓ Uni/multifocal disease
- ✓ Tumor volume: d1 x d2 x d3 x 0.52
- ✓ Veins: renal vein, IVC ++
- ✓ LN (short Ø > 10 mm)
- ✓ Effusion:
  - ✓ Intra- vs retroperitoneal ?
  - ✓ Hemorrhage ?
- ✓ Peritoneum: macroscopic nodules ?
- ✓ Adjacent organs invasion: diaphragm, liver

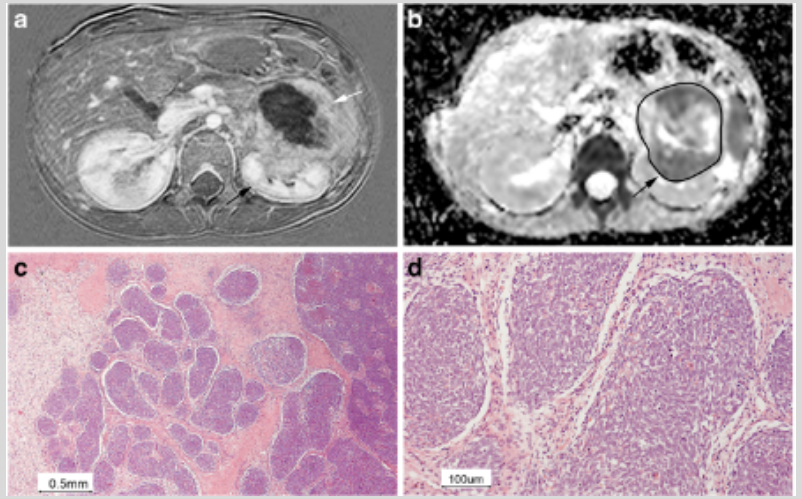
- ✓ Nephrogenic rests: use DWI

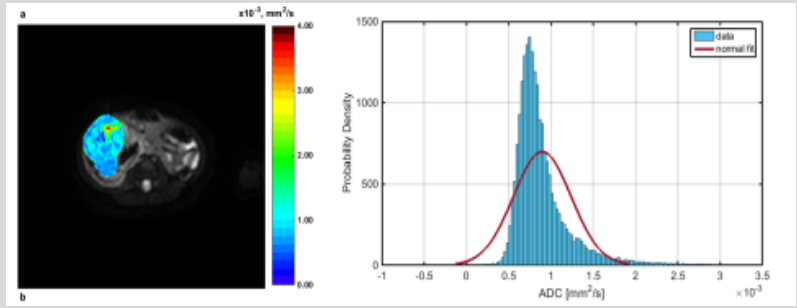
Keypoints for Radiologists: DWI

- **Correlation between post-chemo ADC and histology**
  - Inverse relationship $_{25thp.}$ADC / blastemal components
  - Linear relationship $_{med}$ADC / Stromal components

- **Detection of HR-post-chemo blastemal type**
  - Significant association with initial $_{25thp.}$ADC
  - Significant association with initial ADC histogramm (skweness & kurtosis)*

➢ **More research is needed** on larger databases



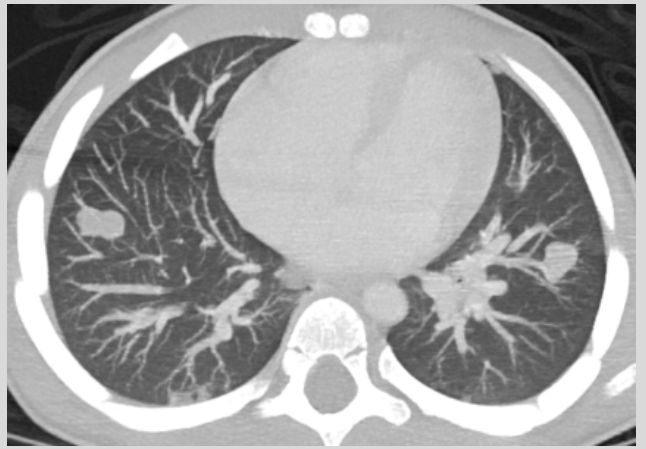


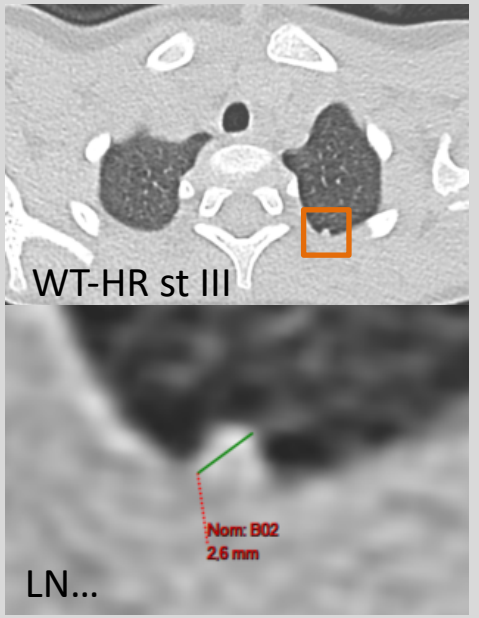
*Hötker AM, Mazaheri Y, Lollert A, **Schenk JP**, Zheng J, Capanu M, Akin O, Graf N, Staatz G. DW-MRI and histogram analysis: assessment of response to neoadjuvant chemotherapy in nephroblastoma. **Abdom Radiol** (NY). **2021**

Littooij AS, Sebire NJ, **Olsen OE**. Whole-tumor ADC measurements in nephroblastoma: Can it identify blastemal predominance? **J Magn Reson Imaging 2017**

Littooij AS, et al. ADC as it relates to histopathology findings in post-chemotherapy nephroblastoma: a feasibility study. **Pediatr Radiol. 2017**

Keypoints for Radiologists: Lung metastases





- **Technique**
  - **Lung CT is mandatory** for all
  - **Dose** adjusted / BMI
  - **MIP** reconstruction / detection (~ 5 mm)

- **Interpretation key points**
  - ✓ Lung « nodules » versus « non-specific » (atelectasia, condensation, calcified granulomas, obvious perifissural LN)
  - ✓ If lung nodules :
    - ✓ Number/location and precise measurements (zoom++)
    - ✓ Four groups : 1-2 / 3-5 / 6-10 / > 10 mm
    - ✓ **≥ 3 mm** leads to neoadjuvant chemotherapy intensification (VA **+ Doxo**)
    - ✓ Reporting: if < 5 mm avoid the term « metastases », prefer « nodules »

Keypoints for Radiologists: Lung metastases

- **Target** nodules: **≥ 5 mm, ≤ 3 nodules, largest axial Ø**
- **Response** criteria : adapted from RECIST

Target lesion (≥ 5 mm)	Non-target lesion	Overall response
CR	**CR**	CR
No rest lesions > 2 mm and no new lesion	**Non PD or SD and no new lesions**	VGPR
> 30% response and no new lesion	**Non PD and no new lesions**	PR
SD and no new lesion	**Non PD and no new lesions**	SD
> 20% increase or new lesions	**PD or new lesions**	PD

SIOP-RTSG – Stage IV - RANDOMET trial

- International randomized phase III **trial** (opening soon)
- **Stage IV** pediatric renal tumors (3 m- 18 y)
- **Lung** metastases (+/- others)
- 29 centres, n= 400 pts
- PIs : Drs A Verschuur (Fr) & Rhoikos Furtwängler (Germ)
- **Rational: to reduce toxicities** (i.e., cardiac/Doxo, lung/RT and liver/Act.D)
- **Primary aim**:
  - Chemotherapy regimen : V**CE** vs V**AD** (std 6 weeks AVD)
    - VCE (vincristin-Carboplatin-Etoposide)
    - VAD (vincristin- Actinomycine –Doxorubincine)
  - *Non-inferiority* study (in terms of metastatic response rate)
- **Primary endpoint** : **% of patients in CR/VGPR** > 6 weeks neoadjuvant chemotherapy

Conclusion - take home messages

- **Achievements**
  - ✓ Better involvement within RTSG (Radiology panel, First Radiology CRF !)
  - ✓ Clear Guidelines
  - ✓ Reporting improvement/harmonisation
  - ✓ National organisation

- **Current challenges**
  - Technical challenge : DICOM data center, DICOM exchange
  - Organisational challenge :
    - Central radiological review in every countries
    - Networking / international collaboration / human resources !!

- **Future = IT**
  - ➢ Research from e-CRF database (correlation with clinic, pathology, genetics)
  - ➢ Research from DICOM international database
  - ➢ International review / studies