

Newsletter



Renal Tumour
Study Group

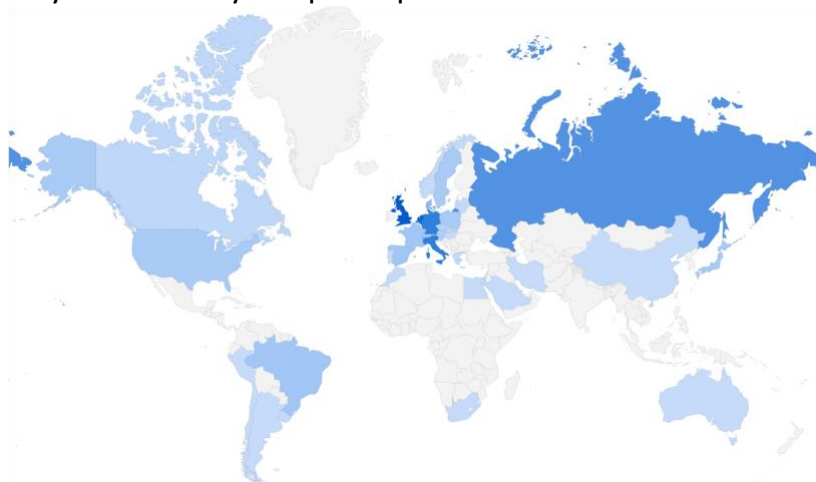
Issue 4 December 2018

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Editorial

SIOP-RTSG is an increasing scientific community with now 44 countries expressing their interest in participating in the upcoming UMBRELLA research study. This is on one side exceptionally encouraging, telling us that we are going in the right direction in aiming to offer all children, adolescents and young adults with kidney tumours the same standardized high-quality diagnostics and treatment, independent of the tumour type, the socio-economic status or the geographic region where the patient lives. And on the other side we are facing new challenges in meeting all the expectations from the members of our community as well as from patients and parents, and overcoming multiple administrative and bureaucratic hurdles in running such big studies as UMBRELLA. SIOP-RTSG is thankful to our friends in North America running trials for kidney tumours in COG with whom we share our vision to cure all children with these tumours around the world. Together with them we are trying to harmonize our efforts to gain the best for our patients in the shortest possible time frame. Together with all of you we are indeed a worldwide community as shown by the participants at least at one of our meetings:



We hope you enjoy this newsletter with a lot of interesting topics. It is great to have you all with us.


Norbert Graf


Gordan Vujanic

UMBRELLA Study

By Norbert Graf



Now it is time to start the UMBRELLA study after a lot of discussions and updating of the protocol as well as the CRFs. The administrative issues regarding Sponsorship and ethical approval are solved. Sponsor of UMBRELLA is the Saarland University, Germany (HOM-01-Klin-2017). Contracts with participating countries are ready. The protocol and other important documents are available for participating centres in the Intranet of our website under <http://www.siop-rtsg.eu/>. Financial issues need to be solved by the participating countries. The IT infrastructure will open soon, so that access to remote data entry and a DICOM server for uploading of imaging studies is given. This will be ALEA or ObTiMA. Training for the use of the IT infrastructure will be provided.

Here are the steps that needs to be done to open the trial in your country or hospital:

1. For each of the participating country a Principal Investigator (PI) for the study and reference centres for radiology, pathology, biology, radiotherapy and surgery need to be established. It is important that this information is given to the sponsor of UMBRELLA. This will be done online by registration to the Intranet you will have access to the following website with a link for the participation in the UMBRELLA protocol as a National / Regional Group:

In the internal section of SIOP-RTSG several means for information and interaction are provided.

Please chose where you want to go (Intranet Menu) →

☞ Participation in the UMBRELLA protocol as a National / Regional Group

☞ Participation in the UMBRELLA protocol as a Local Hospital

2. All participating local hospitals can use the second link on this page to enter the relevant information about the responsible people in their hospital. This is an important information, as this information will be used to get access to the IT infrastructure.
3. You need to translate the information sheet and the informed consent in the language of your country. This is already done for some countries. We would like to get these translations as we will put them in the intranet, so that everybody can get access to these documents in case they are treating a patient from abroad speaking another language than the own one.

4. The PI of the National or regional group needs to get ethical approval for the participation in the study.
5. The PI of the National or regional group needs to sign the contract with the sponsor. This contract will be found on the Intranet and it will be sent to all participating PIs.
6. As soon as the contract is signed access to the IT infrastructure will be provided to those who are listed in the Participation documents as mentioned under point 1.
7. There will be teaching material available for the usage of the IT-infrastructure.
8. Each participating centre has to **enroll every patient with a renal tumour** into this study.

Minimal requirements for participating as a partner institution are

1. Providing full data sets by registration in the remote data system, ALEA or ObTiMA
2. Organised pathology review on a national / regional level, as per the UMBRELLA Study
3. Organised radiology review on a national / regional level, as per the UMBRELLA Study
4. Abdominal MRI (alternatively CT abdomen) and CT scan of the chest as a standard diagnostic approach for each child and for assessment of response in patients with metastatic tumours

Countries that can only meet criteria 1 and 2, are welcome to register patients and to use the therapeutic guidelines. For each patient quality criteria are collected for further analysis. Central pathology review is mandatory for inclusion in any kind of analysis and it should be, preferably, rapid central pathology review.

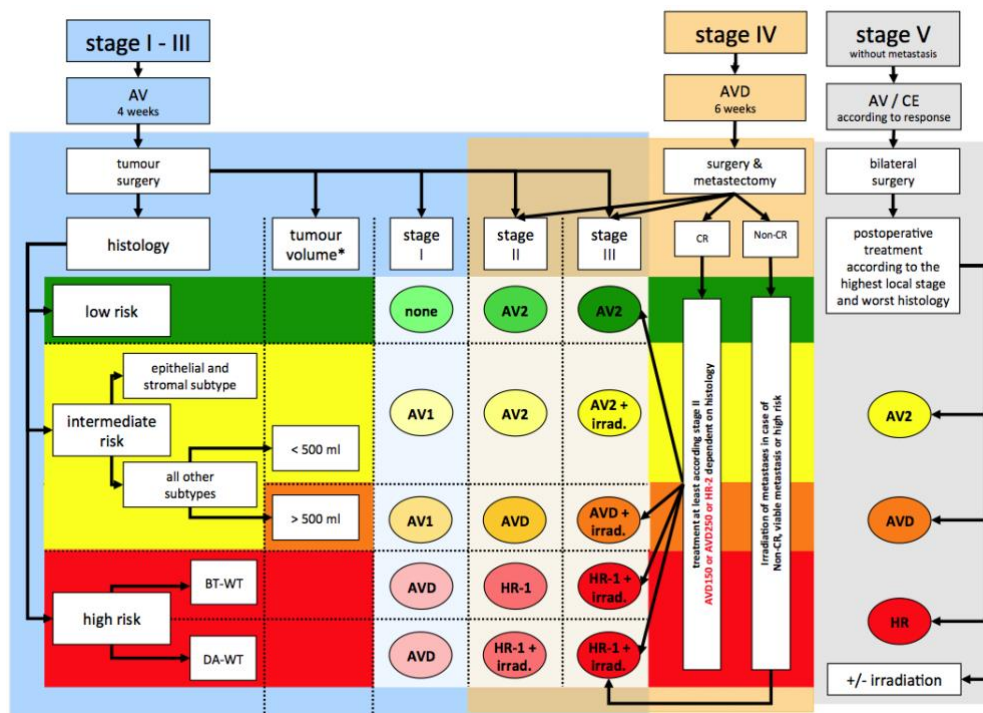
Requirements for enrolment in the final analysis of research questions

In all countries with functional biobanking structures the submission of at least one sample of frozen tissue with corresponding control (blood or adjacent normal kidney in case of nephrectomy) is mandatory. However, it is strongly recommended that biobanking is organized on a national level. The following table provides details on biomaterial requests:

Material (type)	Volume	Processing	Storage (locally)	Shipping †	Research project	Day 0	Day 15 [§]	Prior to / at surgery	Week 1 after surgery	End of treatment	At relapse	
MINIMUM REQUIRED FOR PARTICIPATING IN UMBRELLA AT DIAGNOSIS AND RELAPSE												
A	Tumour tissue (multiple sampling)	≥3 x 1cm ³ blocks	None	-80°C	To national biobank or coordinating center			X			X	
B	Healthy kidney tissue (if available)	2 x 1cm ³	None	-80°C								1q gain analysis
C	Blood for DNA (EDTA)	5ml	None	-80°C								DNA biobanking for other biomarkers/NGS
ADDITIONAL STUDIES (OPTIONAL)												
D	Blood with separation (EDTA)	5ml	Centrifuge for 10min at 1600 xg, separate cellular and plasma fraction	-80°C	To national biobank or coordinating center	X	X	X	X	X	X	
				-80°C								Cellular and cell free DNA, somatic changes (National biobanks)
E	Blood (PAXgene™)* and Serum	2.5ml 1ml	Store upright at room temperature (18-25°C) for 2-72 hours before storage in -80°C	-80°C	To Saarland University: In batches, 1x every 3 months, on dry ice	X	X	X	X	X	X	
F	Urine (cryo tube)	2x2ml	None	-80°C	To Saarland University: In batches, 1x every 3 months, on dry ice	X	(X)	(X)	(X)	(X)	X	
G	Urine # (sterile/centrifuge container)	50ml	None	-80°C	To national biobank or coordinating center	X					X	
H	Tumour tissue	≥1 x 1cm ³	Fresh material ** at 4°C	immediate shipment	To national biobank or coordinating center			X			X	
I	Healthy kidney tissue	≥1 x 1cm ³	Fresh material at 4°C	immediate shipment	To national biobank or coordinating center			X				
J	Blood/DNA from parents (EDTA)	10ml	None	-80°C	To national biobank or coordinating center							

* Tubes will be provided by Dr. E. Meese. § in addition Day 28 in case of stage IV-V disease. † Relevant addresses see below.
 # In some participating countries collection of urine for proteomics / organoid culture may be asked for.

Even as the UMBRELLA study is a research project and no treatment question is asked a standardized treatment for all patients is provided and shown below as a flowchart for nephroblastoma based on the SIOP 2001 trial. Part B of the protocol provides concrete schedules for all kidney tumours in children, adolescents and young adults.



For further details, please visit our website at <http://www.siop-rtsg.eu/>. Information will also be given via mails on a regular basis. Invitations to our yearly meetings are provided to all members of SIOP-RTSG for updating news.

Randomet

By Arnauld Verschuur & Rhoikos Furtwängler



The SIOP RTSG is preparing a randomized multi-centre open-label non-inferiority phase 3 clinical trial for patients with a stage IV childhood renal tumor comparing neoadjuvant Vincristin, Actinomycin-D and Doxorubicin (VAD, standard arm) with neoadjuvant Vincristin, Carboplatin and Etoposide (VCE, experimental arm). The main objective is to determine non-inferiority of neoadjuvant 6 weeks of VAD as compared to 6 weeks VCE in the overall metastatic response rate in newly diagnosed stage IV renal tumour. The analysis will include pulmonary response rate (PRR) and the response rate on non-pulmonary metastasis (NPRR). The rationale of the study is to reduce the cumulative doses of anthracyclines and actinomycin-D from first line treatment of metastatic nephroblastoma and as a consequence to reduce the incidence of (potentially life threatening) side effects (sinusoidal obstructive syndrome (SOS), cardiac sequelae). Vincristin, Carboplatin and Etoposide (VCE) are efficacious and established drugs in nephroblastoma treatment. In addition VCE may be efficacious against histological high risk features such as diffuse anaplasia, blastemal residual volume and gain of 1q chromosome in the renal tumor. However, Secondary Malignant Neoplasia (SMN) may occur with etoposide-containing regimens, but is considered exceptional (<1%).

Metastatic Response Rate (MetRR) is considered as a good surrogate endpoint of outcome (event free survival (EFS)/overall survival (OS)) in stage IV nephroblastoma since patients with complete remission of metastases after preoperative chemotherapy have a far better outcome (OS > 90%) as compared to partial or non-response.

Central radiological review (CRR) will be used at diagnosis, using CT-scan ± abdominal MRI that will identify more reliably the patients who are indeed metastatic and require the appropriate treatment for stage IV tumors. Moreover CRR will be useful for the response assessment in order to choose the adequate postoperative treatment strategy among the several chemotherapy regimens ± radiotherapy.

In addition several histological (stage and risk group of renal tumour, blastemal residual volume) and biological (1q gain, p53 mutations, amplification of Nmyc) will be assessed after either of both arms.

The design of the study will be a randomized phase 3, open-label, international, multi-centre trial with non-inferiority design, with 203 patients/ arm. The expected number of centers: ± 160 centers within ± 14 countries of the SIOP-RTSG network. The expected trial duration will be 6 years + 2 years follow-up. A stratification is envisaged on size of the nodules, Pulmonary mets (PM) only vs. Other Mets (OM) ± PM and country/group.

The main inclusion criteria will consist of children <18 years suffering from metastatic renal tumour at initial diagnosis, having at least one circumscribed, non-calcified (pulmonary) nodule (or other lesion highly suspicious of metastasis according to criteria for metastatic disease) ≥ 3 mm as determined by chest CT-scan and abdominal CT-scan/MRI. Metastatic disease must be confirmed by central review.

The preoperative treatment will consist of VAD (standard arm) versus VCE (experimental arm). The postoperative treatment will be adapted to histology risk group and to response to pre-operative treatment and will include chemotherapy ± radiotherapy.

The German Society of Pediatric Hematology and Oncology (GPOH) will be the international sponsor. The approval of the German competent authorities has been obtained in July 2018. A financial support request has been submitted to the German Krebshilfe (assessment ongoing). A financial support has been obtained from the French National Cancer Institute. National sponsorship is in preparation in 14 countries. The trial is anticipated to open second half of 2019.

The results of this trial is likely to be of interest to all collaborative groups treating pediatric patients with metastatic renal tumours, and potentially also useful for the treatment of localized renal tumours.

More information can be obtained from Arnauld Verschuur (arnauld.verschuur@ap-hm.fr) or Rhoikos Furtwängler (Rhoikos.Furtwaengler@uks.eu), the chairs of the stage IV subcommittee and both Principal Investigators of the RANDOMET trial.



IT Framework

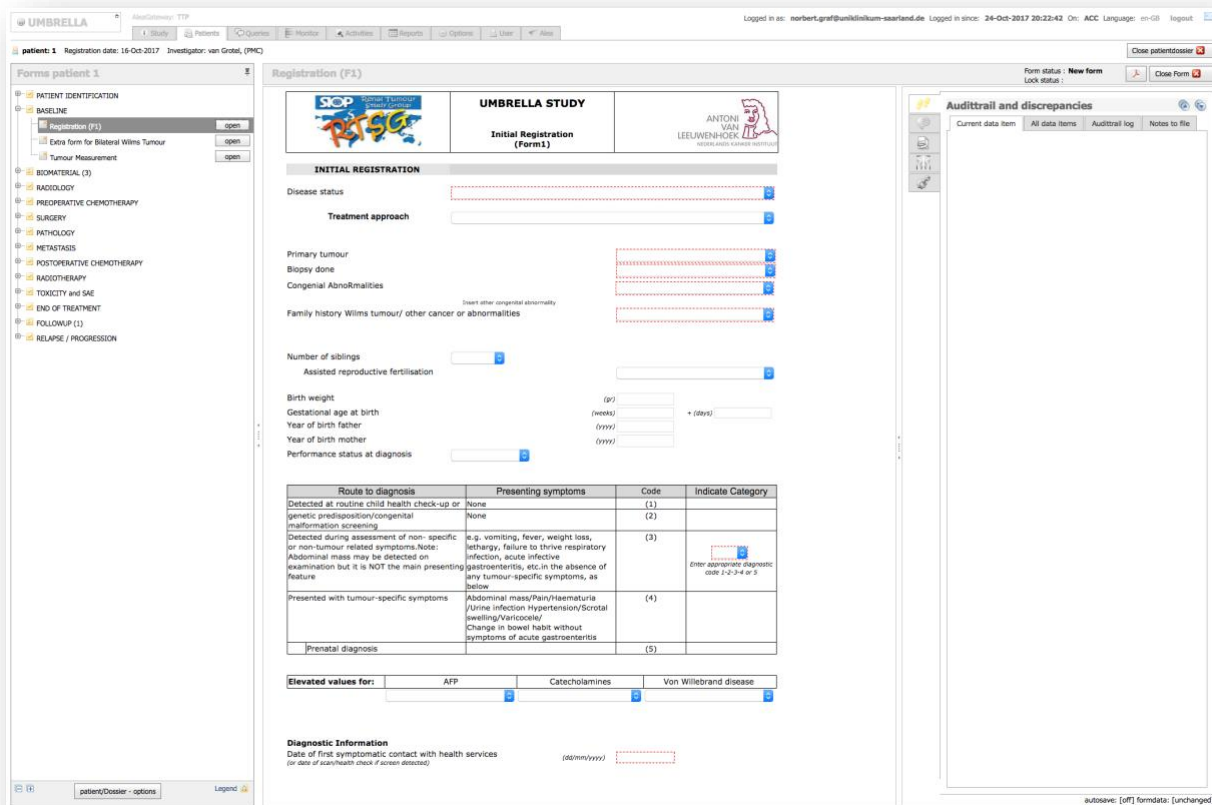
By Harm van Tinteren



Background

For the SIOP-UMBRELLA study, ALEA (<https://www.aleaclinical.eu/>) has been chosen as electronic data capturing system (EDC). The history of ALEA has been described in detail in a previous newsletter available at the SIOP-RTSG site (October 2017).

ALEA is now in use for over three decades by more than 45 organizations for over 800 clinical trials. There are over 10.000 clinical users and more than 50.000 patients included. ALEA contains all the features for data capturing and logging, but also includes an integrated solution for incorporating imaging objects such as CT, PACS and MRI scans into the clinical trial patient dossiers. This DICOM image viewer can be used in many different scenarios. ALEA provides an advanced notification system where for instance research nurses are notified to upload new images, or surgeons are reminded that they are requested to perform an evaluation including a link to the appropriate form to be completed. The most recent version, version 18.1 has just been released and is fully compliant with the EU General Data Protection Regulation (GDPR) that came into force on 25th May 2018. Knowing that the data need to be stored and be available for at least 15 years and that more than 260 institutes around the world will be participating, data management is a serious challenge. Since the 5th of April 2018, ALEA Clinical, within FormsVision is officially an ESCROW certified organization. This certificate is concluded to ensure and secure the use of ALEA Clinical licensees. Escrow is typically requested by a party licensing software (the licensee), to ensure maintenance of the software. The software source code is released to the licensee if the licensor files for bankruptcy or otherwise fails to maintain and update the software as promised in the software license agreement.



Data management infrastructure for SIOP-UMBRELLA.

All data management activities regarding this study will be performed according to the Harmonized Tripartite Guideline for Good Clinical Practice 1997 (ICH-GCP) guidelines and its integrated addendum (E6-R2), and protocol version 1.8, dated May 2017. Central Data Management will be organized by the Princess Maxima Center in the Netherlands. Details about the infrastructure are described in the Data Management Plan version 1.6 (dd 25-09-2018). The data management plan gives a detailed description of the development of (e)CRFs, screen and check validation procedures, study preparation activities, patient enrolment, roles and responsibilities, time lines, data cleaning and reporting processes etc.

Upon registration for the UMBRELLA SIOp Study, a center has to decide whether they want to function as National / Regional Group or as Local Hospital (site). In principle, each country will have one National Data Center, organizing the data management for their own and other individual sites within a country. All sites within a country will be in contact with the National Data Center. Before a site can participate enrolling patients they need to provide a list with full details about the relevant personnel needing access to (parts) of the database and to what extent (different roles). This information will become available in the site delegation log (template forms available at the web site). Training will be provided before using the system and instruction videos will be available through the SIOp web site. Forms in the EDC system can be saved, submitted and eventually locked (by different people with different roles).

Privacy and data protection

GDPR is the most the most important change in data privacy regulation in 20 years. Because data is collected on young children it will not be possible to collect pseudonymised data only. For example, in children we would like to collect the full date of birth which is usually not allowed (is considered personally identifiable). ALEA has built in several specific privacy enhancing technologies: infrastructural technologies such as fire walls and intrusion detection, technologies at database level such as encryption, technologies at application levels such as password policies and end user device based options such as access control based on IP addresses for client devices. Details are available for those who are interested or those that need to provide more information to their local authorities. It may be clear that, although these features are important and applicable, they may hamper easy setting up a site. However, with the construct of National Data Centers and an overarching Data Center in the Netherlands we will be able safely collect a rich set of clinical useful information.

Molecular studies – An update

By Manfred Gessler



As we are getting closer to the official start of UMBRELLA in many participating countries, it is time to re-emphasize the urgent need to improve biobanking as an integral part of the study. In the previous 2017 newsletter we have presented the analysis of chromosome 1q gain as a primary aim of the study and its extension to include analysis of genome-wide copy numbers and loss of heterozygosity. We will soon contact all colleagues responsible for biobanking in each of the participating countries for open questions on collection protocols and estimates of samples that are expected to become available each year.

Our wish list for Biobanking

Beyond the mandatory tumor and normal kidney / blood collection, we strongly encourage all participating centers to provide additional samples for upcoming research questions. Details on sample types and time points can be found in the sample collection table. The latest version can always be found on the SIOp-RTSG web site. Optimal sampling includes: (1) the separation of blood into plasma and cell fraction; (2) multiple blood sampling, before chemotherapy and at several time points before and after surgery; (3) multiple sampling of tumors to catch heterogeneity; (4) diligent and complete sampling of all metastases and relapse cases; (5) special attention to familial and syndromic cases, where the need for genetic analysis is obvious; (6) additional, more specialized samples may be asked for in countries where research infrastructure and sample processing capabilities are in place.

Especially for these rare and heterogeneous pediatric kidney tumors we need a concerted effort to build large enough biobanks to provide solid evidence for future optimization of medical care. The examples detailed below show that such efforts are well under way and productive.

TRIM28 – a new Wilms tumor predisposition gene

The list of familial Wilms tumor genes has had a new addition with the identification of inactivating *TRIM28* mutations in familial Wilms tumors.¹ *TRIM28* is known as an epigenetic regulator of developmental gene expression and it interacts with *REST* and *WTX/AMER1*, genes that are also mutated in Wilms tumors.²⁻⁴ Although based on a limited number of cases, the key features of *TRIM28* mutant tumors are quite intriguing. They seem to be characterized by an earlier onset, epithelial histology, a lack of *TRIM28* immunoreactivity and excellent prognosis. The ease of identification of tumors that may be *TRIM28* mutant by histology and immunostaining should facilitate collection of larger numbers of cases to provide definitive answers on their clinical course that may guide future clinical decision-making.

Genetic basis of CMN

The *ETV6-NTRK3* translocation has long been associated with congenital mesoblastic nephroma (CMN)⁵ and a recent larger scale study by Vokuhl et al.⁶ provided clear evidence that only the cellular subtype of CMN carries this genetic change. No genetic cause for classical and mixed CMN had been found so far. This has changed with the identification of stereotypic *EGFR* intragenic tandem duplications (*EGFR-ITD*) that are characteristic for these subtypes.⁷ The duplication involves the kinase domain and leads to activation of the MAP kinase pathway. Several of the cases that lacked this alteration showed functionally related mutations leading to the activation of *BRAF* through gene fusions or deletion of the *BRAF* negative auto-regulatory domain. Although this rare tumor entity can often be cured by surgery alone, these molecular genetic findings offer the chance to use novel targeted therapies in advanced and more difficult cases.⁸

Liquid biopsy shows great potential

A pioneering study by Jiménez et al.⁹ demonstrated that tumor derived DNA makes up a significant fraction of circulating DNA in the blood of Wilms tumor patients. Even from small amounts of blood plasma they could perform whole exome sequencing to identify copy number variations and small mutations present in the tumor.

A prime application for liquid biopsy tests for circulating tumor DNA (ctDNA) would of course be diffuse anaplastic Wilms tumor with its high prevalence of *TP53* mutations. Treger et al.¹⁰ could convincingly show that these *TP53* mutations can be detected in plasma-derived ctDNA before nephrectomy and levels dropped after surgery as expected. If confirmed at a larger scale, this will open up the possibility to classify pediatric kidney tumors immediately at diagnosis with the chance to adapt therapy early on. These results also hold great promise for future longitudinal sampling to follow tumor response and to aid in early detection of relapse.

References:

- Halliday, B.J., et al., *Germline mutations and somatic inactivation of TRIM28 in Wilms tumour*. PLoS Genet **14**: e1007399 (2018). [PubMed](#)
- Wegert, J., et al., *Mutations in the SIX1/2 pathway and the DROSHA/DGCR8 miRNA microprocessor complex underlie high-risk blastemal type Wilms tumors*. Cancer Cell **27**: 298-311 (2015). [PubMed](#)
- Mahamdallie, S.S., et al., *Mutations in the transcriptional repressor REST predispose to Wilms tumor*. Nat Genet **47**: 1471-4 (2015). [PubMed](#)
- Kim, W.J., et al., *The WTX Tumor Suppressor Interacts with the Transcriptional Corepressor TRIM28*. J Biol Chem **290**: 14381-90 (2015). [PubMed](#)
- Knezevich, S.R., et al., *ETV6-NTRK3 gene fusions and trisomy 11 establish a histogenetic link between mesoblastic nephroma and congenital fibrosarcoma*. Cancer Res **58**: 5046-8 (1998). [PubMed](#)
- Vokuhl, C., et al., *ETV6-NTRK3 in congenital mesoblastic nephroma: A report of the SIOP/GPOH nephroblastoma study*. Pediatr Blood Cancer **65**: (2018). [PubMed](#)
- Wegert, J., et al., *Recurrent intragenic rearrangements of EGFR and BRAF in soft tissue tumors of infants*. Nat Commun **9**: 2378 (2018). [PubMed](#)
- Drilon, A., et al., *Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children*. N Engl J Med **378**: 731-739 (2018). [PubMed](#)
- Jimenez, I., et al., *Circulating tumor DNA analysis enables molecular characterization of pediatric renal tumors at diagnosis*. Int J Cancer (2018). [PubMed](#)
- Treger, T.D., et al., *Somatic TP53 Mutations Are Detectable in Circulating Tumor DNA from Children with Anaplastic Wilms Tumors*. Transl Oncol **11**: 1301-1306 (2018). [PubMed](#)

Pathology

By Gordan Vujanic



The UMBRELLA Study is about to start recruiting patients, and pathology is going to play a major role in the Study. To remind you, **rapid** central pathology review is mandatory for all participating countries in the UMBRELLA Study. It was successfully done in the UK, France and Germany during the SIOP 2001 Trial, and proved to be very valuable in ensuring that children are treated appropriately according to their tumour type and stage. As explained previously, this will be delivered by the National/Regional Pathology Panels as follows:

Egypt	Naglaa el Kinaii (naglaa_elkinaai@yahoo.com)
France (SFCE)	Aurore Coulomb-L’Hermine (aurore.coulomb@aphp.fr)
Germany (GPOH)	Christian Vokuhl (cvokuhl@path.uni-kiel.de)
Italy (AIEOP)	Paola Collini (Paola.Collini@istitutotumori.mi.it)
Japan (JWITS)	Yukichi Tanaka/Hajime Okito (ytanaka@kcmc.jp; okita-h@heio.jp)
Northern European countries	Ellen D’Hooghe (eldhoo@ous-hf.no)
Poland	Jozef Kobos (jkobos2012@gmail.com)
South America	Isabela Werneck Cunha (iwerneck0210@gmail.com)
Spain (SEHOP)	Enrique de Alava (enrique.alava.sspa@juntadeandalucia.es)
The Netherlands (DCOG)	Ronald de Krijger (R.R.deKrijger@umcutrecht.nl)
United Kingdom (CCLG)	Gordan Vujanic (gvujanic@sidra.org)
SIOP (all other countries)	Gordan Vujanic (gvujanic@sidra.org)

So, all national PIs should inform their pathologists about this, and they should establish a contact with a chair of the Pathology Panel who will be dealing with their cases. Some countries enquired whether they could have their own Pathology Panels – it is fine if they want to form these panels, and send cases to them so they may develop additional expertise and experience by seeing more cases, but this can only be done on an informal basis and it is NOT a substitute for the official rapid central pathology review which can only be done by the designated Panels as above. Cases should be sent to the Panels with no delay, even if you are unsure whether or not a patient will be eventually registered in the Study. The Panels will be dealing with all cases in the same manner, and you will have their opinion as quickly as possible.

A paper on the UMBRELLA pathology and molecular biology protocol has been recently published (*Nat Rev Urol* 2018, Nov;15(11):693-701, doi.org/10.1038/s41585-018-1000-3) and it is available for downloading on the SIOP-RTSG intranet site. Again, the national PIs should distribute this paper to their pathologists for better understanding of the criteria for sub-classification and staging of tumours, which have changed in comparison to the SIOP 2001 Trial.

News from the Radiology Panel: CRR, practical considerations

By Anne MJB Smets



Centralized radiology review (CRR) is one of the major steps forward of the UMBRELLA protocol, leading to standardization of imaging interpretation and consequently improving the stratification of patients.

CRR consists of a “real time” or “rapid” (within 96 hours) review of the imaging studies by an independent radiologist with expertise in renal tumours in children. Within UMBRELLA, CRR has been organized on a national basis: each participating country has appointed a referent radiologist who will review the imaging studies of all renal tumour patients in his/her country.

CRR is applied at 3 time points (and also whenever recurrence is suspected):

1. At diagnosis, on all available chest and abdominal imaging studies to confirm a renal tumour and determine if the disease is uni- or bilateral and/or metastatic.
2. Pre-surgery: on abdominal imaging for localized disease and on abdominal and chest imaging for patients with metastatic disease (stage IV)
3. At the end of treatment

Double reading will increase the quality of interpretation of the imaging studies which will automatically improve the assessment at diagnosis and of treatment response.

For countries where this particular expertise is not available CRR will be performed by a member of the RTSG expert radiology panel.

Current SIOP-RTSG-Radiology Expert Panel

Anne Smets (Chair, The Netherlands)

Hervé Brisse (France)

Henrique Lederman (Brazil)

Carlo Morosi (Italy)

Øystein Olsen (UK)

Jens-Peter Schenk (Germany)

The panel will also carry out independent review for patients treated in the referent radiologists' centre. Furthermore, the panel provides expert opinion for selected difficult cases and also aims at improving the technical quality of the imaging studies by providing detailed radiological guidelines and giving feedback. Feel free to contact the panel for guidance and for answering questions related to imaging in general.



News from the Radiotherapy Panel Further Steps of Integration of Modern Irradiation Concepts and Techniques

By Christian Rübe and Patrick Melchior

Radiotherapy is still an important and integral part of the multimodality curative treatment concept in Wilms tumours for children. The main concepts of postoperative radiotherapy from the previously SIOP-2001 study remain, so that only a few modifications are recommended in the new Umbrella protocol. Mainly there are several new recommendations and modifications in dose prescription depending on the histology risk group for the whole abdomen, whole lung and liver, lung recurrences and other metastatic lesions.

In Umbrella the centralized radiotherapy review by the national and the central radiotherapy panels will be a major future step in the standardization of the use of radiotherapy and integration of new modern techniques like IMRT, 4D-CT and VMAT. In preparation for a prospective multicentre study to compare standard RT-techniques with modern intensity modulated irradiation techniques with or without a reduced target volume to the flank with dose sparing concepts of organs at risk the RTSG-Radiotherapy Panel is preparing an amendment for Umbrella especially for this question.

Current SIOP-RTSG-Radiotherapy Panel

Christian Rübe (Chair, Germany)	Patrick Melchior (Germany)
Geert Janssens (The Netherlands)	Daniel Saunders (United Kingdom)
Davila Fajardo (The Netherlands)	Farid Alam (United Kingdom)
Aymeri Huchet (France)	

The knowledge about the patterns of recurrence in the previous SIOP trials, especially in SIOP-2001 is an essential tool for the standardized use of these reduced target volumes with intensity modulated techniques. Therefore, the study group from Homburg, Germany reported on the international SIOP congress in Washington in October 2017 and the German Radiooncology Congress in June 2018 (DEGRO) about the first results of the clinical outcome in children with unilateral intermediate- and high-risk Wilms tumours after multimodality treatment following the SIOP-2001 GPOH study with special regard to the postoperative abdominal radiotherapy and local control. In conclusion the data show that children with Wilms tumours treated with a postoperative abdominal radiotherapy (PORT) have an excellent local control, especially in the intermediate-risk subgroup. The evaluation of irradiated vs. eligible but nonirradiated children suggests that local radiotherapy to the tumour bed is of considerable impact for local control in different risk groups and remains a prognostic parameter. Most local relapses occur inside the radiation field, are combined with distant metastases and resulted in a poor clinical outcome. So actually, the postoperative radiotherapy concept is still the standard of care in selected children after preoperative chemotherapy and surgery when risk factors are available.

Furthermore the Radiotherapy Study Groups from Utrecht, Netherlands and Homburg, Germany initiated in 2017/2018 an interobserver multicentre trial with eleven European radiotherapy centres participating in the Netherlands, France, Germany, Belgium, Denmark, Italy, Norway, United Kingdom and Portugal to survey the interobserver variability regarding the contouring guidelines in the amendment protocol .

Surgery

By Jan Godzinski



Surgery was the first effective treatment for nephroblastoma. First descriptions of successful operations were published at the end of XIX century. In early XX century, Ladd and Gross markedly modified technique of surgical resection. They recommended wide transabdominal approach and early ligation of renal vessels. These rules apply until today. Explored in several SIOP studies, the preoperative chemotherapy appeared very effective, and in together with high definition imaging (CT and MRI) invented several ideas of new surgical approaches. Number of those possibilities will be tested in our new study called UMBRELLA.

Partial nephrectomy: this technique was proved to be safe and effective in both unilateral and bilateral cases if adequately selected. The benefit of preserving as much renal parenchyma as safely possibly makes the whole treatment less harmful. The basic condition to consider this technique is sufficient vascular supply of the part of the kidney planned to be spare. Vessels must not cross the tumour mass and the portion of kidney planned to spare should be reasonable big.

Laparoscopy is another technique rapidly developing. - Of course, the tumour nephrectomy may be performed also this was. The minimally invasive procedures, are however reserved for smaller tumours and should not be performed in patients eligible for partial nephrectomy. All the classical requirements of the oncological nephrectomy must be fulfilled, mainly gentle management of the tumour and adequate sampling of the regional lymph nodes.

IVC problems: Surgery faces also extreme challenges like IVC, atrial or heart thrombus. Thrombus reaching the level of hepatic veins or higher should be handled in together with cardiac surgeons, at their OP theatre using C-P bypass. Surprisingly high proportion of those very difficult cases are successfully treated, however need to be referred to very experienced multidisciplinary centres.

Relapses and metastases: Surgery in nephroblastoma also deals with relapses and metastases. Still there are no clear recommendations regarding surgery for relapse. Majority agrees, that it should be performed after a response to chemotherapy is achieved and only exceptionally can be nephron sparing (relapse of low or intermediate risk histology tumour in the unique kidney). Metastases, which are usually located in the lungs, frequently disappear after chemotherapy alone, but in case of their persistence, metastasectomy may be both the curative and the diagnostic tool. An information on how vital is the metastasis is of utmost importance. If this aim dominates, surgeon should consider thoracoscopic approach as less harmful to children. In case of clearly single or few subpleural lung metastases, this technique can also be used as curative one.

Technical novelties like CUSA, harmonic knife or water-jet knife are not crucial for quality of surgery but may facilitate resections, save the time and decrease the blood loss.

ERN: The experience of centres appears more important than tools. In Europe, one of the fields of activity of the European Commission is European Reference Network (ERN Paed-Can for paediatric oncology). This system take care of the trans-border health care, advisory boards for difficult cases and trans-border for some most challenging which cannot be treated in their countries. One of the fields of ERN Paed-Can is oncological surgery for most difficult and complicated cases of renal tumours. Number of high-quality centres were designated to play the role of the "centres of excellence" and accept such patients.

Surgical subcommittee: The SIOP RTSG committee has several panels of experts or subcommittees. Each sub-group is responsible for its field. Also, surgeons are working in such a group composed of number of paediatric surgeons experienced in the oncological surgery. The group meets once or twice a year, but constantly communicates electronically regarding scientific projects, ongoing study and difficult cases.

Some participating countries

Italy

By Filippo Spreafico



The *Associazione Italiana Ematologia Oncologia Pediatrica* (AIEOP) has conducted three cooperative studies on renal tumors since 1981 (*Consiglio Nazionale Ricerche* (CNR)-80 and -92 protocols, and TW2003).^{1,2} The treatment benchmark in Italy has remained immediate nephrectomy followed by adjuvant therapies, but the use of preoperative chemotherapy (originally prescribed for cases considered at higher risk of surgery-related morbidity or tumor spillage) has significantly increased over time, and ‘outside’ protocol recommendations (preoperative chemotherapy was given to 42% of patients in the last protocol).

The results of the previous CNR92 protocol showed areas for potential improvement in some subgroups of patients (the EFS rates for patients with WT stages III and IV were 74% and 50%, respectively, and 64% for patients with anaplasia); cardiopulmonary toxicity prevention; and protocol organization and quality control issues. The Italian cooperative study TW2003 aimed to ameliorate central pathology review process and biological studies. A specific protocol aim was to organize a renal tumor biological and histological sample banking platform for diagnostic and research purposes: the proportions of cases submitted for central pathology review (82%) and biological studies (57%) was seen as a significant improvement over the past, and gave rise to different research projects (biomarker discovery studies, basic research on WT development, mechanisms towards tumour progression and metastization, familial tumours).

TW2003 protocol registered children with primary intrarenal tumors from 34 AIEOP-affiliated hospitals, from July 2003 to January 2015 (of 656 children recruited, 471 had unilateral WT). The TW2003 treatment regimens compared favorably with contemporary SIOP/COG studies, and were better than the former CNR92 protocol, despite a reduction in the therapeutic burden for some patients (Figure 1).²

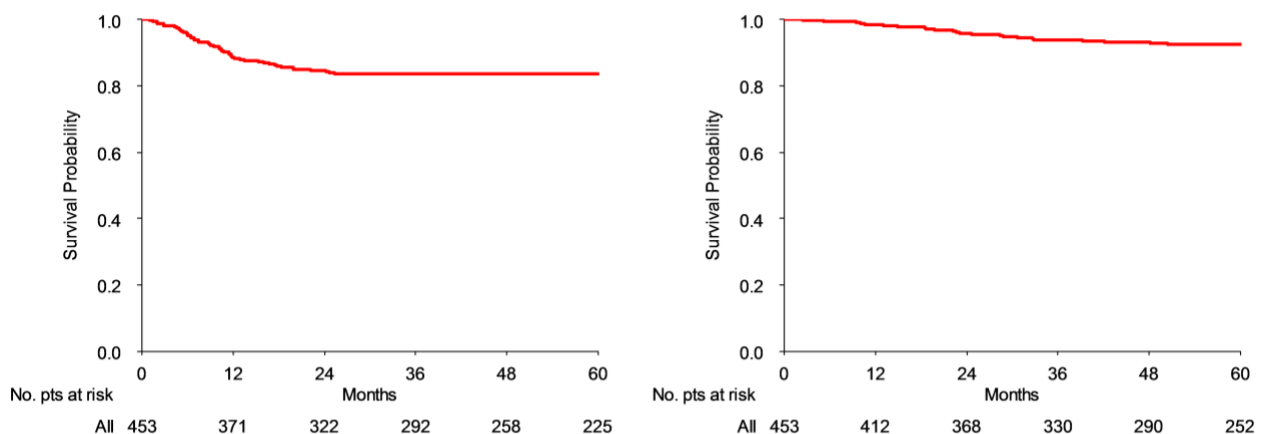


Figure 1. The 5-year EFS and OS estimates were 83.7% (95%CI: 80.2%–87.3%) and 92.4% (89.8%–95.1%) for the whole series.

The group has critically recognized that a major weakness of the approach to using preoperative chemotherapy under the TW2003 lies in that histological assessment of *in vivo* tumor response (as in the SIOP approach) was only partially considered for the purposes of a more risk-adapted treatment for children given preoperative chemotherapy. This is one of the reasons why the group has taken the important decision of participating for the first time in a SIOP protocol for renal tumours.

Ready to 'introduce' in the SIOP family, the AIEOP Renal Tumour Working Group has now evolved towards an attempt to have more structured central pathology review (chaired by P. Collini, pathologist), central radiology review (C. Morosi, radiologist), central tissue banking (Daniela Perotti, biologist), and sharing of difficult cases, basing on multidisciplinary case discussion with experts in the field [L. Gandola, radiation oncologist, D. BIASONI, surgeon, and pediatric oncologists who have developed interest and skills in renal tumours: A. Serra (Roma), G. Bisogno (Padova), M. Terenziani and F. Spreafico (Milano), A. Di Cataldo (Catania), P. D'Angelo (Palermo), M. Bianchi (Torino), M. Nantron (Genova), M. Di Martino (Napoli)].

Noteworthy, since last year AIEOP set up a national wide pre-paid transportation system to central reference laboratories, to improve logistic for each AIEOP hospitals, sending histological samples for central pathology review purposes, hopefully for all pediatric cancers. The system is connected to the central CINECA-AIEOP database platform, allowing reference pathologist to link their report to all the other patient clinical records.

The group is ready and really thanks the SIOP RTSG to welcome all of us!

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Portugal

By Nuno Reis Farinha

The Portuguese Society of Pediatric Hematology and Oncology (SHOP) will participate in the SIOP RTSG protocol UMBRELLA. Despite all the problems we have to integrate the international studies, SHOP is committed to join the SIOP cooperative groups.

Portugal has 4 Pediatric Oncology Units, all recognized by the Ministry of Health as National Reference Centers, located in the following Institutions: The University Hospital São João in Porto, The Portuguese Institute of Oncology in Porto, the Pediatric Hospital in Coimbra and the Portuguese Institute of Oncology in Lisbon. All Units agreed to participate.

Portugal has 10 30 000 inhabitants. We have approximately 15-20 children and adolescents per year with renal tumors and we hope that soon we will be registering them all in UMBRELLA.



Egypt

By Wael Zekri

The largest two centers dealing with the pediatric oncology cases in Egypt will participate for the first time in the SIOP-RTSG studies. These two centers are the National Cancer Institute, Cairo University and the Children Cancer Hospital in Egypt (CCHE- 57357 hospital) and they are both located in Cairo. Around 120 cases are expected to be recruited from those two centers yearly. Some other centers are willing to participate from other places such as Alexandria and Assiut with around 60 cases yearly and they might be involved latter on.

Two groups from all the different specialties were included in both centers, including surgeons, pathologists, pediatric oncologists, radiotherapists, radio diagnosis, clinical and basic research. They were meeting regularly to study the UMBRELLA protocol and to be oriented with the implementation process.



Dr. Gordan Vujanic visited Egypt in February 2015 to speak about the pathology details and approach in SIOP, also he met with our pathologists in both centers and discussed the issue of the central pathology review. Also Dr. Norbert Graf visited Cairo in November 2017 and 2018 and gave an orientation about the UMBRELLA protocol and the prerequisites to start recruiting the patients.

The Telepax and the bio bank facilities and staff are available in both centers. Telepax can help reviewing the radiology of some difficult cases to establish the diagnosis and staging, also the preserved tissues in the bio bank can help in further biological studies

Norway

By Marta Maria Burman

There are four pediatric oncological departments in Norway, all of which will be recruiting patients for the UMBRELLA study. The study is approved by the ethical committee, and the approval applies to all centers. We will be ready to start recruiting patients shortly. Norway's population is quite small, we expect to enroll about 6-8 patients per year. The biological samples will be stored in the national biobank at Oslo University hospital. The reference pathologist for northern Europe, Ellen D'Hooghe, is also located at Oslo University hospital, and this makes central pathology review a smooth process for Norwegian patients. The Nordic countries have a long history of close collaboration through the NOPHO (Nordic society of paediatric hematology and oncology) network, and this has certainly been fruitful when it comes to the preparation of the UMBRELLA study. We are hoping to have the radiological department at the hospital in Lund, Sweden, a center for central radiology review for the Nordic countries, but this is an ongoing process and not yet established.



Singapore

By Prasad Iyer

KK Women's and Children's Hospital is the only integrated children's hospital in Singapore and provides pediatric oncology care for about 70% of local children. We expect 5-10 children with renal tumors will be part of the study annually from our center. We have applied for and obtained local institutional IRB approval to join the SIOP-RTSG UMBRELLA study. Since mid-2018, we have been using UMBRELLA as the reference protocol for the last few renal tumors that we have treated in our center.

Our radiology department will be providing multi-modality state-of-the-art imaging and aiming to participate in central radiology review. Prof. Gordan Vujanic has kindly agreed to help us with central pathology review. Percutaneous biopsies are performed by our team of pediatric interventional radiologists and pediatric surgeons. We hope to be able to contribute to the biology studies and have planned for frozen samples to be sent to respective centers in Europe in batches. We have done tumor banking as well as patient-derived cultures and xenografts, and will be happy to explore supporting these research initiatives as well.

Singapore has a multiracial population, and while English is the standard medium of communication, Chinese is used by a large part of the population. Thus, informed consent forms have been translated into standard simplified Mandarin Chinese ("pu tong hua") and sent to RTSG.

We are new to the SIOP RTSG, and greatly appreciate the warm welcome to this group. We look forward to contributing to the scientific community in whatever way we can and participating in this study.



IMPORT Report

By Kathy Pritchard-Jones and Reem Al-Saadi



IMproving Population Outcomes for Renal Tumours of childhood (IMPORT) is an observational UK & ROI study funded by EUFP7 and has served as a forerunner for the UMBRELLA study.

IMPORT's aim is to maintain the success of first line therapy whilst improving risk stratification to reduce the burden of therapy for the overall population of children and young people with Wilms Tumour and other renal tumours of childhood. The IMPORT study includes biological characterisation of tumour, blood (and plasma) and urine samples to better define the molecular pathways involved, particularly in high risk, 'blastemal type' Wilms tumour.

Since rapid central pathology review was successfully introduced in SIOP UK 2001 Trial, it continued in the IMPORT study. It is also a pilot study that has tested the feasibility of Central Radiology Review (CRR) at a national level in the UK for the first time. Imaging (CT and MRI scans) performed in 'real time' are reviewed to standardise assessment of diagnosis and response to treatment and to test the feasibility of integrating all of these complex datasets within e-health. The latter aims to improve clinical decision making in a future clinical trial. Registered patients are treated according to the current standard approach to risk stratification and treatment arms defined on the recently closed phase III clinical trial run by the International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group (RTSG).

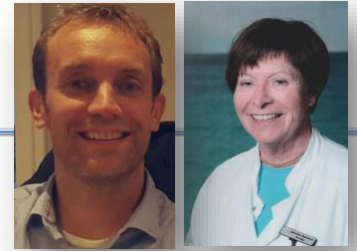
It has also tested the feasibility of collecting multiple tumour samples from the nephrectomy (or tumour resection) and blood and urine from 5 different timepoints from time of diagnosis until the end of treatment. We have developed and standardised the methodology to allow serial sample collection of blood and urine at set time points: at diagnosis, mid treatment, pre nephrectomy, post nephrectomy and end of treatment, (and at relapse if applicable). In addition, we also collect frozen tumour and its mirror FFPE block from multiple nephrectomy sites and normal kidney, as well as when applicable, metastatic and relapse tissue. To date we have collected a total number of 6670 samples from 450 patients registered in the 20 UK CCLG centres. This includes 834 frozen nephrectomy tumour samples collected from 17 centres from 255 patients, and 803 paraffin-embedded tumour blocks from 245 patients. 81% patients provided frozen tumours and 78% paraffin tumours from 2 tumour sites or more. Most have provided matching normal kidney as well. 318 patients from 20 centres have provided cell fraction and plasma out of which 70% come from at least 2 timepoints. In addition, we have 1,317 frozen urine samples, 81 frozen biopsies, 21 paraffin biopsies, and 5 relapse samples stored.

The study opened in October 2012 and is ongoing. It has registered 591 patients so far and the plan is to integrate this into the UMBRELLA study as part of the larger sample size required for clinical validation of gain of 1q as an adverse biomarker. The collection of patient samples, radiology images, and also patient's data in the form of Case Record Forms (CRFs) has been very successful with the 20 UK CCLG centres cooperating and adhering to the IMPORT manual.

The results of the study have been presented at various meeting and congresses, and published in full in peer reviewed journals (see the SIOP publication list).

SIOP-RTSG meeting, Copenhagen, 2018

By Jesper Brok and Catherine Rechnitzer (local organizers)



This year more than 150 colleagues from 31 different countries participated in the SIOP-RTSG 2018 meeting in Copenhagen (11-12 June). Colleagues from Europe, South and North America, China, South Africa and Singapore with an interest or expertise in renal tumors managed to soldier all the way to Scandinavia. Hence, it was a privilege being the host but also some busy weeks planning the meeting. We were fortunate that the *Danish Child Cancer foundation* and the *Danish Cancer Society* supported the meeting, which ensured us excellent and central facilities. We therefore hope that all participants enjoyed the city and the venue.

As always Marry and Norbert chaired the inspiring presentations and discussions in a friendly and open-minded way; the meeting highlights were that after - a massive work-effort - the new *UMBRELLA* protocol is finalised and, on the cusp, to be launched. The meeting revealed that an impressively high number of countries and centres will participate and they are currently preparing CRF's, ethical approval and considering what adjacent research they will be involved in. We can only encourage to register (www.siop-rtsg.eu/) and start the preparation as there might be some additional challenges due to the enforcement of the EU data protection law. However, we hope that this will not delay participation. Furthermore, the design for the adjoining randomised trial (*Randomet*) for metastatic disease (Stage IV) was likewise presented and the trial is in its final preparation.

As usual it was captivation to hear our COG colleagues present their latest data and protocol refinement incorporating step by step use of molecular biomarkers in risk stratification and also to get an update about clinical trial development in Japan. Finally, the Wilms tumor project in Africa informed us that a significant treatment improvement can be achieved despite very limited resources in some African countries.

With best wishes and hoping to see you all next year.

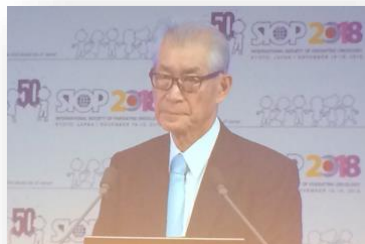
SIOP-RTSG meeting, Prague, 2019

<https://www.siope.eu/activities/siopes-upcoming-events/siope-2019-congress/>



The SIOP-RTSG Meeting will be held during the SIOP Europe Annual Meeting 2019 in Prague. The foreseen dates are Thursday and Friday, 23rd and 24th of May 2019. An Agenda will be provided shortly. Participation is only possible by invitation. All members of SIOP-RTSG will receive such an invitation by SIOP Europe.

SIOP Congress Kyoto



From 16th to 19th of November the 50th Annual Meeting of SIOP was held in Kyoto Japan. At that meeting we had great and informative sessions dealing with nephroblastoma. One of the highlights was the keynote lecture given by this year's Nobel Laureate for medicine Prof. Dr. Taksuku Honjo. His excellent and stimulating talk about PD1 and PD-L1 was outstanding.

At the congress on the 16th of November we had a closed Meeting of SIOP-RTSG with participants from many countries around the world. The topic was about the new UMBRELLA protocol and administrative issues. All this information is given in this newsletter on page 2 and 3. In addition, Conrad Fernandez did present an update of the 1q gain results in the COG renal tumour studies and how they will use 1q gain in their upcoming trials for stratification. As 1q gain is the major research question in UMBRELLA these data are of utmost importance for our group. Janna Hol presented a summary of the WAGR meeting held together with and organized by the parent's group for WAGR in Ann Arbor at the 19th and 20th of October 2018.

Here are some impressions:



SEE YOU THERE!
Lyon, France | October 23-26, 2019

In conjunction with:

See you all again in Lyon at SIOP 2019

In Memoriam Dan D'Angio

By Beatriz de Camargo

"His eyes have closed. They will open in a better world than this."

—Audrey Evans, September 14, 2018

I had the great privilege of having Dr. D'Angio as a mentor during my career, and the greater privilege of being a part of his international family. Known as "Dan", he was always ready to help. He expressed continual interest in what you were doing, and shared ideas with great enthusiasm. Over thirty-six years of friendship, we never let a year pass without seeing each other, and sharing at least one dinner together. Upon my first arrival in Philadelphia in 1982, Dan quickly welcomed me into his family and I had one of the most wonderfully fruitful years. After that, he visited Brazil four times, and all of my family and friends became part of his "fan club".

He pioneered the concepts of cooperation among groups, and of the multidisciplinary team. As Chair of the National Wilms Tumor Study (NWTs) since 1969, he introduced the practice of combining different cancer treatments for maximum effectiveness. In his 1972 paper on Wilms tumor treatment, he described the importance of "solidarity" and "various specialty groups working together" for progress in treatment methods.

Dr. D'Angio was responsible for the creation of the Brazilian Wilms Tumor Study Group. For our first trial, he challenged me to make it simpler than what the NWTs study was doing. At that time, the NWTs-4 wanted to determine whether actinomycin could be given as a single dose using the pulse-intensive schedule. However more questions were investigated, requiring more patients. The Brazilian Wilms Tumor study group performed a trial with one single question; patients of all stages were randomized to have only one difference in the schedule—standard fractionated dose vs. single dose—and we were able to analyze our results before the NWTs-4. I remember him calling me and saying, *"I knew what you were doing, but you were not supposed to publish before us, but I am very proud! Congratulations!"*

With his slogan *"Cure is not enough"*, he highlighted the importance of late effects, insisting that quality of life is as important as survival. In 1997, he created the NWTs Late Effects Study Group. He never stopped. As he always said, *"the clock is still ticking for us"*.

He was responsible for introducing me to several international pediatric oncology colleagues, and most importantly to SIOP meetings. One day, we were having lunch at his home and he suddenly said, *"You have to cross the Atlantic, and go to the SIOP meeting next September in Berne, Switzerland."* I attended the SIOP meeting in 1982, which allowed me to expand my view of pediatric oncology worldwide, and especially of different approaches to Wilms tumor treatment. When the Brazilian Wilms tumor group emerged to the SIOP Wilms tumor group, he said *"I am not supposed to like this, but I am sure you are in the right direction. Go ahead!"*

More people like him are needed, not only in pediatric oncologist societies, but throughout the world. He has made a tremendous difference for children with cancer in many countries. The current success in Wilms tumor treatment is due to his strength, and dedication to the introduction of group cooperation and multidisciplinary teams.



Publications

2018

POSITION PAPER: THE UMBRELLA SIOP-RTSG 2016 STUDY PATHOLOGY AND MOLECULAR BIOLOGY PROTOCOL

Vujanic G, Gessler M, Ooms A, Collini P, Coulomb-l'Hermine A, D'Hooghe E, de Krijger R, Perotti D, Pritchard-Jones K, Vokuhl C, van den Heuvel-Eibrink M, Graf N

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THE ROLE OF TCF3 AS POTENTIAL MASTER REGULATOR IN BLASTEMAL WILMS TUMORS

Kehl T, Schneider L, Kattler K, Stöckel D, Wegert J, Gerstner N, Ludwig N, Distler U, Tenzer S, Gessler M, Walter J, Keller A, Graf N, Meese E, Lenhof HP

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HIGH DOSE TREATMENT FOR MALIGNANT RHABDOID TUMOR OF THE KIDNEY: NO EVIDENCE FOR IMPROVED SURVIVAL – THE GESELLSCHAFT FÜR PÄDIATRISCHE ONKOLOGIE UND HÄMATOLOGIE (GPOH) EXPERIENCE

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IRINOTECAN FOR RELAPSED WILMS TUMOR IN PEDIATRIC PATIENTS: SIOP EXPERIENCE AND REVIEW OF THE LITERATURE; A REPORT FROM THE SIOP RENAL TUMOR STUDY GROUP (RTSG)

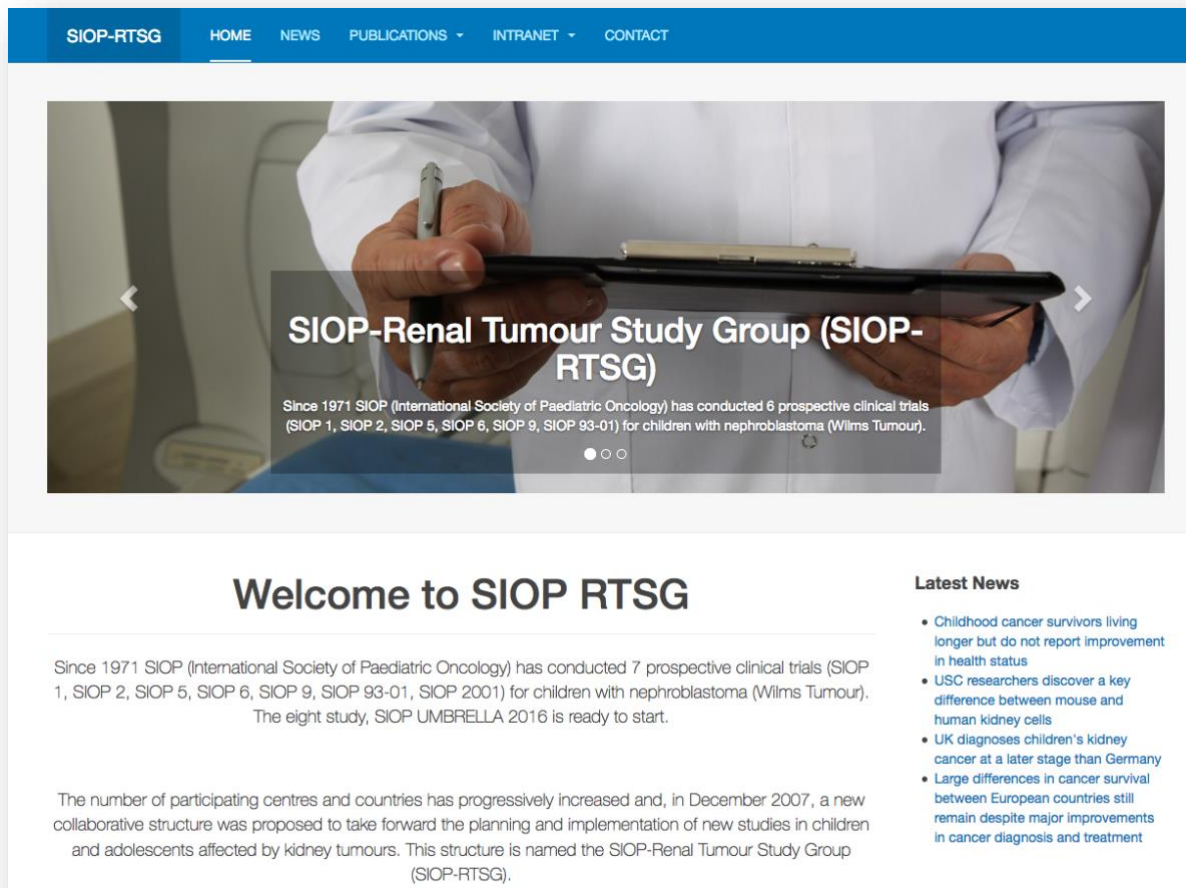
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POSITION PAPER: RATIONALE FOR THE TREATMENT OF WILMS TUMOUR IN THE UMBRELLA SIOP–RTSG 2016 PROTOCOL

Van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones KJP, van Tinteren H, Fürtwängler R, Verschuur AC, Vujanic GM, Leuschner I, Jesper Brok, Rübe Ch, Smets AM, Janssens GO, Godzinski J, Ramírez-Villar GL, de Camargo B, Segers H, Collini P, Gessler M, Bergeron Ch, Spreafico F, Graf N on behalf of SIOP-RTSG
 Nature Reviews Urology, 2017; <https://www.nature.com/articles/nrurol.2017.163>

Our Website

Please visit our website. Here you can find a lot of interesting information. Members of SIOP-RTSG can create an account for the Intranet, where the UMBRELLA protocol, CRFs and other news are shared.



SIOP-RTSG HOME NEWS PUBLICATIONS INTRANET CONTACT

SIOP-Renal Tumour Study Group (SIOP-RTSG)

Since 1971 SIOP (International Society of Paediatric Oncology) has conducted 6 prospective clinical trials (SIOP 1, SIOP 2, SIOP 5, SIOP 6, SIOP 9, SIOP 93-01) for children with nephroblastoma (Wilms Tumour).

Welcome to SIOP RTSG

Since 1971 SIOP (International Society of Paediatric Oncology) has conducted 7 prospective clinical trials (SIOP 1, SIOP 2, SIOP 5, SIOP 6, SIOP 9, SIOP 93-01, SIOP 2001) for children with nephroblastoma (Wilms Tumour). The eight study, SIOP UMBRELLA 2016 is ready to start.

The number of participating centres and countries has progressively increased and, in December 2007, a new collaborative structure was proposed to take forward the planning and implementation of new studies in children and adolescents affected by kidney tumours. This structure is named the SIOP-Renal Tumour Study Group (SIOP-RTSG).

Latest News

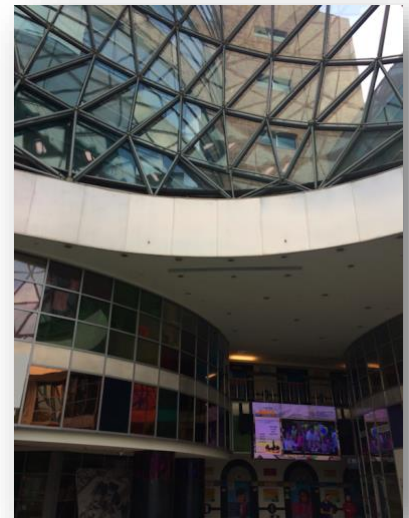
- Childhood cancer survivors living longer but do not report improvement in health status
- USC researchers discover a key difference between mouse and human kidney cells
- UK diagnoses children's kidney cancer at a later stage than Germany
- Large differences in cancer survival between European countries still remain despite major improvements in cancer diagnosis and treatment

Further News

After the SIOP-RTSG Meeting the UMBRELLA protocol was presented at several conferences and meetings in Moscow, Cairo, Shanghai and Guangzhou by Norbert Graf.

From the 25th to the 26th of October 2018 the **VII Russian Pediatric Oncology Congress “Achievements and Prospects of the Pediatric Oncology”** did took place in Moscow. The UMBRELLA protocol was discussed and participation in the study is foreseen, if the administrative hurdles are overcome. At the conference Norbert Graf gave a talk entitled: “State of the art of renal tumours in childhood”.

In Cairo the **International conference “Bridging Gaps in Oncology”** was held from the 7th to the 9th of November 2018. Norbert Graf gave a talk about the update on renal tumors in childhood including educational cases. During a visit to the 57357 hospital on Saturday the 10th of November a fruitful meeting with discussions about participation in the UMBRELLA study was held with the study team of Renal Tumors headed by Prof. Dr. Wael Zekri and Prof. Dr. Sherif Abullnaga as the CEO of the hospital. As a result, SIOP-RTSG is happy that the Renal Tumour Group from Cairo is joining the UMBRELLA protocol.



57357 Hospital in Cairo

During a visit in **Shanghai and Guangzhou** Norbert Graf had important meetings in China to discuss their participation in the UMBRELLA protocol. In Shanghai he discussed the topic with the Team of Prof. Dr. Dong from the Children’s Hospital of Fudan University. It is decided that they will go through all the administrative issues and apply to ethical approval to be able to join the UMBRELLA protocol.

From the left: Prof. Dr. Xiaowen Zhai, Prof. Dr. Norbert Graf, Prof. Dr. Kuirand Dong, Dr. Rui Dong

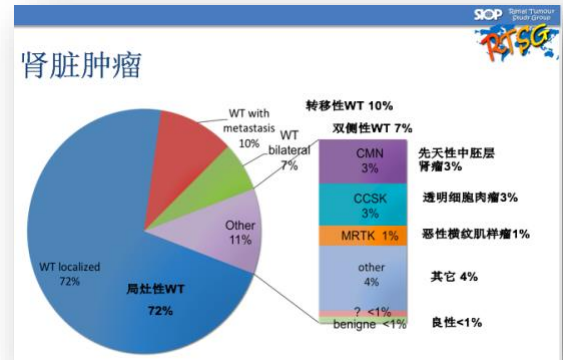


Meeting in Guangzhou:



In Guangzhou an International Conference on Childhood Solid tumors was held from the 1st to the 2nd of December. Norbert Graf did participate in this conference by giving a talk about the State of the Art of Renal Tumors in Childhood. In advance of that conference Profs. Dr. Xiaofei Sun and Dr. Yizhuo Zhang organized an excellent meeting in Guangzhou at the Sun Yat-Sen University Cancer Center & Department of Pediatric Oncology and invited doctors from different hospitals in China and also from different disciplines, including pediatric oncologists, pediatric surgeons, pathologists, radiologists, radiotherapists and others. Participants were from:

- Sun Yat-Sen University Cancer Center
- Sun Yat-Sen University the First Affiliated Hospital
- Xinhua Hospital Affiliated Shanghai Jiaotong University School of Medicine
- Tianjin Medical University Cancer Institute & Hospital
- Guangzhou Women and Children’s Medical Center
- Shenzhen Children's Hospital
- Beijing Children’s Hospital, Capital Medical University
- The Children's Hospital, Zhejiang University School of Medicine



The topic of the interactive meeting was the feasibility of joining the UMBRELLA protocol. Having had a visit to all the facilities of the Department of Pediatric Oncology at the Sun Yat-Sen University Cancer Center Norbert Graf is convinced that they fulfill all requirements to participate in the UMBRELLA study, including biobanking and a clinical trial center. The biggest hurdles are financial and administrative issues. But with their impetus they are able to overcome these logistic problems.

They are keen to set up reference centers for pathology and radiology for the centers that will join the upcoming Chinese Renal Tumor Study Group that is intended to establish very soon. SIOP-RTSG will support them in all possible aspects. All agreed at the end of the meeting that it was very successful and that further meetings will come.



The Sun Yat-Sen University Cancer Center in Guangzhou

Upcoming Meetings

12 th to 15 th of April, 2018	Denver, Colorado, United States	COG Spring Group Meeting
29 th March to 3 rd of April, 2019	Atlanta, Georgia, United States	AACR Annual Meeting 2019
23 rd to 24 th of May, 2019	Prague, Czech Republic	SIOPT-RTSG Committee Meeting
31 st May to 4 th of June 2019	Chicago, IL, United States	ASCO Annual Meeting 2019
23 rd to 26 th of October, 2019	Lyon, France	51th Congress of SIOPT

Impressum

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