Editorial

It is with great pleasure to present you the 7th SIOP-RTSG Newsletter. Although we all hoped that the COVID-19 pandemic could be overcome in 2021, but this was not the case. Nevertheless, we can look back on a very successful 2021 for our Renal Tumour Study Group. UMBRELLA is now recruiting patients for more than 2 years and the number of patients enrolled is already higher than 1200, and they are coming from 20 different countries as shown in the following figure from the last Newsflash of November 2021.

Despite all the administrative and bureaucratic regulations, we are proud to announce that RANDOMET as a randomized trial can now start very soon to recruit the first patients with metastatic nephroblastoma.

During this year we were also very active in setting up an Association of SIOP-RTSG and on the 16th of June this year we were able to celebrate the foundation. This is a big step that will help us to optimize our SIOP-RTSG group. In the near future you will receive an invitation to get a member of the Association. The first general assembly will be held at our next annual meeting in Sevilla in June 2022. Hopefully Corona allows us to meet you all in person and not only virtual.

Within this newsletter you will get an update of our work during 2021. We hope you find it interesting to read.

Now, being at the end of the year, we wish you a Merry Christmas and a healthy New Year, for you, your families and friends, most important stay healthy!

Norbert Graf
Gordan Vujanic
The first patient was recruited in June 2019 into our UMBRELLA study. Up to now 20 countries are registering patients and more are under initiation. During these 30 months 1234 patients are enrolled, and each month between 50 and 70 new patients enter the study. Regular Newsflashes are prepared by the data management in Utrecht and is available in the Intranet of our website. Due to the Covid-19 pandemic, we anticipate that there may be some registration delays.

Here are again the logistics before we can initiate a new country:

1. The National coordinator needs to provide the following:
   a. Completion of registration of the full team on the intranet. A template is found at our website: [http://siop-rtsg.org](http://siop-rtsg.org).
   b. Ethical approval needs to be obtained.
   c. The Sponsorship contract with Saarland University needs to be signed. A template can be found in the intranet of our website.

2. Initiation will then start
   a. The SIOP-RTSG Office will plan an initiation visit by Zoom
   b. All people that will enter data will get access to the ALEA database by the SIOP-RTSG Office

3. After initiation of a country the national/regional coordinator of the country has the following duty:
   a. Initiation of local sites

As UMBRELLA is a research study trying to find new biomarkers for a better stratification of patients in upcoming trials, we put a lot of energy into ongoing biological and add-on studies. These studies deal with molecular biology, radiotherapy, radiology, pathology, etc. To get an overview of research results of former and current projects please have a look on the publications of SIOP-RTSG as presented at the end of this Newsletter. We encourage our members to participate in these research projects.

Another important issue is the fact that UMBRELLA is the 8th clinical study or trial. In 2021 we celebrated the 50th anniversary of the SIOP Renal Tumor Study Group. This was presented in an Editorial of the Annals of Oncology. In Figure 1 of this editorial the timeline of a 50-year success story is given.
The randomized controlled trial SIOP-RTSG Randomet 2017, exploring the non-inferiority of upfront Vincristine, Carboplatin and Etoposide compared to standard Vincristine, Dactinomycin and Doxorubicin, is now open in Germany. Eventually, the SIOP-RTSG Steering Committee and the Randomet Team were able to overcome last hurdles. To facilitate real-time radiology-review the internationally established Medical Data and Picture Exchange (MDPE) System was set up for Umbrella and Randomet for German centres and is now productive. Participating centres can upload the initial and subsequent imaging and findings to Prof. Jens-Peter Schenk, Heidelberg and receive the reference findings and the study centres inclusion recommendation within one working day, ideally even on the same day. Also, the contract between the Sponsor GPOH gGmbH and the PMC Data Canter was finalized. Thus, on December 1st 125 local investigators and study nurses from more than 50% of the 47 German centres were initiated by the Randomet Team and the GPOH gGmbH representative. Recruiting can now start, and we are expecting the first patients to be entered within the next weeks. Opening of the remaining German centres is planned for early January 2022 as well as a Kick-Off meeting for France. Further national coordinating centres in Switzerland, Austria and Belgium are ready to be opened subsequently. The national canter in Czech Republic is answering last requests of their national authorities and will follow soon. Spain, Brazil, Netherlands, Italy, and Denmark are at different stages of their submissions and can follow next year. We are also planning to include further interested countries as for example Norway, Sweden, Poland and Greece as soon as possible. Overall, we are aiming to have 2/3 of the planned recruitment rate by end of the next year. Recruitment is planned to last roughly 5 to 6 years with an interim analysis after accruing 50% of patients. As now things gain pace, Arnauld and I hope you are as excited as we are. We also want to thank everybody supporting the project, most notably the Co-Chairs of SIOP-RTSG Prof. M.M. van den Heuvel-Eibrink and Prof. Norbert Graf for their continuous support.
The HARMONICA (HARMONization and CollAboration) initiative, which was started in 2015, represents the efforts of the Children’s Oncology Group Renal Tumor Committee (COG RTC) and the International Society of Pediatric Oncology Renal Tumor Study Group (SIOP RTSG) to formally collaborate to advance clinical effectiveness research. This collaboration aims to enhance efforts for children with renal tumors worldwide based by internationally defining the research agenda based on clinical challenges in the field, putting efforts in defining endpoints in order to compare transatlantic studies, by performing systematic reviews to obtain evidence for clinical recommendations, and where possible, to set up collaborative biological and clinical studies. Connecting multidisciplinary professionals on a global level through stimulating collaborative activities on the level of transatlantic discipline committees and panels is an important way to move this field forward. Last but not least, it has been acknowledged, that investing in future developments in the field will benefit from programs for collaborative training, mentoring and transatlantic exchange of young colleagues (SIOP-E and COG Young investigator initiatives). A driving principle guiding the strategy of HARMONICA’s collaborative efforts, is that it aims to advance research that cannot be successfully achieved by either cooperative group separately (replication, validation, and power issues). So far, several studies on harmonization of standard of care approaches, reviews and biological studies have already been accomplished. Over the past year, fertility after renal cancer, nephrometry, nephrogenic rests and epidemiology were important research topics that have been discussed. Currently, a special issue on the perspectives and challenges for pediatric renal cancers is being prepared by this group, in which over 100 transatlantic collaborating experts will participate.

HARMONICA Chairs:
Prof. Dr. James Geller
Prof. Dr. Marry M. van den Heuvel-Eibrink
Data Management

By Harm van Tinteren, Prakriti Roy, Sandra van der Kroef, Ingrid Schut, Danny Baars, Marry vd Heuvel-Eibrink

The SIOP-RTSG 2016 UMBRELLA database in ALEA is currently available and initiated in 17 countries, and 4 large regional sites (Russia and China) in Europe, South America and Asia. In total that includes 148 active local sites and around 644 users who access the UMBRELLA database across the globe. Altogether over 1300 cases are now registered in ALEA, and on a daily basis the team in Utrecht is available for all issues regarding inclusion and registration issues. Also, queries for missing forms are sent out regularly, and 5 DM meetings were organized with international DMs. Also, in 2021 we started with national coordinators meetings in order to address issues regarding initiation, inclusion and data collection.

The capabilities in ALEA are constantly being expanded based on suggestions and requests from users. Recently, the ability to access the radiological images that can be uploaded to the DICOM server with any viewer as desired was added. This need came particularly from the central review radiologists as they found the available viewer in ALEA too limited. Further, in the Netherlands, the SDV (Source Data Verification) module has been used by monitors of the UMBRELLA data of the Princess Máxima Center cohort. This module will become useful for monitors in the various countries when monitoring data in the Randomet study. This will need to be organized in National Coordinating Centers (NCCs) and monitors will be trained and will get site or country specific access by the data center of the Máxima. This information will be further detailed in the next update of the data management plan (DMP) of UMBRELLA. The updated DMP also has an appendix on CRFs required per disease type. Finally, certain inconsistencies with the country codes have been corrected and the privacy data statement, system access and the data validation section have been updated.

Next to the UMBRELLA database, the Randomet database is ready for registering and randomizing patients eligible for the Randomet study. For the Randomet study, all patients irrespective of ALEA or ObTiMA will be first registered in ALEA, eligibility for Randomet will be checked and if eligible Randomization will be performed. This setup prevents registering patients twice. Data from the Randomet study can be easily merged with the UMBRELLA study data. The randomization process involves a minimization procedure. Stratification factors are country-group, tumor size and tumor location and patients will be randomized between the two arms VAD and VCE.

Another project, currently underway, is the creation of a database of historical SIOP-RTSG data. All data since the SIOP93-01 study have been captured electronically. However, in the 93-01 study, paper CRFs were used and centrally entered into one database, but in the 2001 SIOP study, more countries and centers participated and the paper CRFs were no longer sent to one data center. Instead, a large number of "electronic data capturing" (EDC) systems were used and none were "cloud-based." This meant that the data had to be sent from the NCCs to the data center in the Netherlands at different times. There, the variables and codes had to be mapped to a central system and the data had to be merged. From a maintenance and consistency perspective, this was a very complex and error-prone process. From the central data center, the idea then arose to bring together all the data, totaling some 8,000 kidney patients, into a new cloud-based system, that is similar to the current UMBRELLA database build in ALEA.
A girl who unfortunately passed away in 2020 in the Prinses Máxima Center, after treatment resistant cancer, thought that money should be raised in the context of her funeral to improve pediatric cancer research. Her family made this project possible and donated this private gift for this particular project, called “Minke's Wish project”. Currently, a data scientist at the Maxima is recoding all variables and codes from the 93-01, the 2001 and the UK-import study into an ALEA-database similar to UMBRELLA. This is obviously a huge job due to the multitude of forms with sub-forms and the differences in items and detail therein. Some forms and solutions are discussed with the chairperson of a particular disciplines to make sure that the items are interpreted correctly. In terms of data, of course, the bilateral tumors and forms must again be considered separately. At this moment, the forms of the SIOP2001 have already been largely mapped to those of the UMBRELLA. Next, the data from the sub-EDCs will be read one by one into the parent database. We will approach all NCCs with the question, whether they have any data entered into their system after 2011 (closure SIOP2001 trial) and before UMBRELLA and will then upload the most recent data.

All in all, this “Minke's Wish project”, will bring together the largest international data series in pediatric renal cancer and this will:

- Secure data from previous SIOP-RTSG studies
- Improve quality and security of data storage (GDPR standard)
- Make data sharing and analysis faster and more efficient
- Make inconsistent data and missing data visible so they can be retrieved
- Allow entering follow-up data, so that the database becomes richer
- Ultimately provide better understanding of (very rare) kidney tumours, generate outcomes of specific subtypes and treatments, and identify children who would benefit from change of treatment

Handover of the private funding “Minke’s Wish project”, by the family of Minke at the Princess Máxima Center (13 October 2021)
(Note: Minke's photo with parental permission)
News from Biology Panel
By Manfred Gessler

As we were not able to hold our International Pediatric Renal Tumor Biology Meeting in Marseille, the process of updating each other on progress reached in the different labs has slowed down considerably. We very much hope that 2022 will provide the opportunity to finally meet again in person. There will be plenty of projects to be presented covering topics such as genome sequencing, epigenetic and single cell analyses as well as various modeling efforts and basic mechanistic studies. Plans are in the works for an on-site meeting in Marseille in September / October 2022 – so stay tuned.

Numerous institutions in many countries are now actively collecting biospecimens to enable future research - either locally, in national reference labs or through international exchange of materials. Unfortunately, informed consent for biobanking and especially sampling of frozen tissue and blood samples (listed in Form F5) are still not available in a significant proportion of cases. Informed consent for biobanking is available in only three-quarters of cases, and biobanking has actually been performed in even fewer cases. Please ensure that you collect samples comprehensively as described in the UMBRELLA protocol. For more details, please refer to the Lab Manual (Biobanking Recommendations) available on the SIOP-RTSG web site. A condensed overview is shown in the figure below. In case of uncertainties do not hesitate to contact the Biology group.

Assessment of the relevance of 1q gain and/or blastemal volume for stratification of Wilms tumors are the primary aims of UMBRELLA, and therefore tumor and blood samples are critical to achieve the goals of UMBRELLA. Further preclinical testing of molecular diagnostic tools such as liquid biopsies, or evaluation of possible novel drug candidates depends on prospectively collected and richly annotated cases. This ensures that we can leverage this information for future improvement at all levels.
Pathology Panel News

By Gordan Vujanic

Despite all the problems linked with the pandemic, all national/regional pathology panels have been working very hard and delivering central pathology review. We don’t have the data ready to check what percentage of cases have been sent for rapid central pathology review, but I know that the cases are reviewed promptly, as soon as they reach the responsible panels. We are still expecting some panels to start collaborating (Egypt, for example), and hope that they will start contribution and attending our review meetings soon.

Since the last Newsletter, we manage to have 3 review meetings. The first one was in February 2021, organised by Ronald de Krijger, and it was the virtual meeting, during which we reviewed the Dutch cases. It worked very smoothly, and it showed that virtual/online reviews are possible, and we will probably be using it when other panels obtain the scanning facilities.

The second meeting was in Bonn, in September 2021, organized by Christian Vokuhl, and we reviewed the GPOH cases (~180 cases in total). However, there are another 200+ cases from the GPOH that need to be reviewed, so we will go back to Bonn soon.

The third meeting was in Paris, in December 2021, and we reviewed ~240 French cases, so France is now up to date with their cases. Future review meetings have been planned for 2022, and we hope that by the end of the year, we will catch up with all cases that need to be reviewed.

Our members have published a number of papers on pathology and contributed to other projects (please see the list of publications in this Newsletter).
The radiology panel is the representative of the radiologists involved in research studies of SIOP-RTSG and reference radiology in the current Umbrella study. In continuing the work of 2020, the radiology panel is involved in further projects in 2021/2022:

- The Delphi study (group facilitation technique and an iterative multi-stage process) of the radiology panel designed in 2020 to create consensus statements from expert opinions, was finished and published by Justine van der Beek and Annemieke Littooij in 2021 to determine the value of MR imaging in pediatric renal tumours.

- Based on the study results a group of radiology panel members prepared a study especially with Non-Wilms tumors (rhabdoid tumours and clear cell sarcomas of the kidney) to work out the value of imaging and potential of MRI including dwi in differential diagnosis of these tumours.

- The radiology panel is involved in the strategy of tumor biopsy to define updated rules for biopsy indications. A specific article submitted to PBC by the RTSG is currently under review. Hervé Brisse from Paris (France) is the leading radiologist in the radiology panel in this field of research and will present these new guidelines at the European Society for Pediatric Radiology meeting (June 2022). Reference radiology, biopsy rules and new imaging techniques improve the diagnostic strategy in pediatric renal tumors.

- The Umbrella protocol is characterized by a very high quality of diagnostic reports by central radiology review. This central radiology review is still organized by national radiologists or group of radiologists. Different models for central review are set up in participating countries based on experiences in SIOP 2001, e.g. central radiology review for Umbrella started 2020 in France with 7 pediatric radiologists and Germany continued central review of SIOP 2001 in Pediatric Radiology in Heidelberg University Hospital by one pediatric radiologist. Germany started Umbrella in 2021. In the Netherlands the central review for renal tumours is performed in the Princess Maxima Center since 2019 by one radiologist.

- Reference radiology in participating countries is organized by national groups in different ways in their own responsibility using the F2R forms of the Umbrella protocol.

- Members of the radiology panel participate in cooperation with the COG. Among them there is a participation in the HARMONICA nephroblastomatosis working group. Representative of the radiology panel is Annemieke Littooij from Utrecht / the Netherlands.

- National and planned international review papers with imaging of renal tumors in childhood let the diagnostic strategy be aware in advanced radiology training in the radiological community.

- Members of the panel are involved in clinical studies of the SIOP-RTSG panels. Carlo Morosi from Milano (Italy) is representative of our group in imaging questions to tumor relapse.
Current SIOP-RTSG core group members of the radiology panel:

- Jens-Peter Schenk, Germany
- Hervé Brisse, France
- Annemieke Littooij, the Netherlands
- Henrique Ledermann, Brazil
- Carlo Morosi, Italy
- Ostein Olsen, UK
- Karoly Lakatos, Austria
- Ana Coma, Spain
- Maria Gavra, Greece
- Dorota Slodowska, Poland
- Luc Breysem, Belgium
- Enno Stranziner, Switzerland
- Gabor Rudas, Hungary

All radiologists interested in pediatric renal tumors are very welcome to work with us in the radiology panel of SIOP-RTSG.

Literature:


Radiotherapy treatment in UMBRELLA still plays an important and integral role in the multimodality treatment concepts for renal tumours in children. Successful international implementation of standardized radiotherapy concepts in UMBRELLA will have the potential to improve outcome while reducing long-term toxicities and optimize future data collection.

Over time, more and more radiation departments are gaining access to modern advanced image guided radiotherapy (IGRT) techniques that allow high-precision dose delivery to complex target volumes, minimizing potential adverse effects or late sequelae to surrounding normal tissue. Regarding these advances, we recently published a consensus statement on flank target volume delineation for highly conformal approaches. This guideline has translated well-established standardized conventional radiotherapy techniques in standard of care in kidney cancer applied over decades, into modern highly conformal image guided flank irradiation concepts. These new concepts take into account pre- and postoperative MRI, postoperative changes of the surgical retroperitoneal cavity and organ shift and reduces the planning target volume and therefor the volume of irradiated normal tissue significantly. A single center analysis from Utrecht provides encouraging evidence of the safety of such modified highly conformal target volume concepts in 36 WT patients, eligible for flank irradiation, resulting in comparable low rates of abdominal outfield relapses.

The interobserver multicenter contouring study on flank delineation with radiooncologists from eleven participating European centers initiated in 2017/2018 by the Radiotherapy-RTSG panel group published in 2021 showed a relevant interobserver variability of such a new sophisticated target volume delineation. This result underlines a central quality assurance process as mandatory before the start of radiation treatment. To avoid uncontrolled and heterogeneous global implementation of such new radiotherapy concepts in kidney cancer a prospective observational multicenter study available for centers with a high experience in modern image guided irradiation techniques will be amended to the UMBRELLA SIOP-RTSG-2016 protocol. The interobserver variation and the relevance of target volume reduction will be observed prospectively. Long-term local control and toxicity of these new concepts for registered SIOP-UMBRELLA patients will be followed in a prospective European based multicenter quality assurance study via the QUARTET - platform with a standardized pre-radiotherapy quality assurance review. The radiotherapy panel will provide experts for a specific reviewer pool, who evaluate the quality of contouring and treatment plans via the online RTQA platform in QUARTET before start of radiation treatment. Furthermore, all generated data in QUARTET will be transferred to the RTSG - ALEA database to facilitate future clinical research of radiation-related questions.

Current SIOP-RTSG-Radiotherapy Panel

Christian Rübe (Chair, Germany) Farid Alam (United Kingdom)
Patrick Melchior (Germany) Aymeri Huchet (France)
Geert Janssens (The Netherlands) Emmanuel Jouglar (France)
Davila Fajardo (The Netherlands) Karin Dieckmann (Austria)
Daniel Saunders (United Kingdom) Lorenza Gondola (Italy)
References:


News from the Surgical Panel
By Jan Godzinski

Dear Friends,

The pandemic does not surrender. All we have enormous problems to run effective activity in our important field: people die of COVID-19, but people also keep dying of cancer. That takes a lot of time and focuses emotions.

In my place we were able to “statistically” avoid delays in the anti-cancer surgery, but still, we are facing difficult situations where we do not see any good choice. To be able to help children with cancer, logistics and management appear crucial prioritising the life-threatening diseases as the first in line. Few words on how we manage that in my Department, which may help You or I will be helped by Your ideas how to improve that:

Only PCR-tested patients are admitted:
If the test is negative – the routine work-up is started, but testing is repeated every 72 hrs. All patients are in single-rooms (+mother or father) or at maximum double rooms. If the test is positive but the patient can wait, he/she waits. If this is not possible, the patient is admitted to the buffer section of the department, which is separated from the remaining stations by the locks (every kid stays always with one of the parents). Necessary surgery is conducted with all the precautions but never markedly postponed. The quarantined patients go the same way as COVID positive ones. Parents: if positive – imply the same way for their kids as if they were COVID positive.
This is in brief how we work. That was possible because we were able to close an important part of the Department and use it only as a single-room (not really single – in fact single patient + parent) buffer section. We avoided to have any major internal COVID infection focus up to now. But hernias, cryptorchids etc. are being admitted in low number and the waiting list prolongs …

Anyway, I still do believe that the pandemic will go away or will become less harmful along with the time. We cannot stop all our RTSG activities due this nasty virus. And we did a lot last months!

1. The RTSG consultation platform works like always.
2. Decades of the over-sea discussions with our US friends ended-up in closer and closer co-operation, both on the scientific ground (common surgical papers planned), consultation ground (several cases discussed in common) and Harmonica.
3. RTSG/COG meet on Harmonica webinars systematically. Surgery plays there an important role. ICG use for lung metastasis and sentinel node detection in both open and minimal invasive surgery (led by Max Pachl (RTSG), Marc Wijnen (RTSG) and Hafez Abdelhafiez (COG), and nephrometry and its combination with “Audry formula” are just leading common ideas. The leader from the COG-side is Nick Cost, I take care of the RTSG part.
4. Finally, we have a real perspective for a better data access within RTSG: Harm van Tinteren works for Prinsess Maxima Center and will have more time to help us (!)

Dear Friends,

I miss a lot meeting All of You in person, our discussions in the evenings after meetings and friendly atmosphere we were so happy to develop over the last 50 years.

Never give -up! All those things will come back.

Dear Friends, please accept my best Seasons Greetings: Merry Christmas and Happy, Prosperous New Year for You, Your Families, Friends and Teams.

All the Best!

Prof. J. Godzinski MD PhD
jgodzin@wp.pl
Chair of the Surgical Panel of the SIOP RTSG (Renal Tumours Study Group)
Head of Dept. of Paed. Surgery, Marciniak Hospital,
Fieldorfa 2, 54-049 Wroclaw, Poland
+48-71-3064389 (secr), +48-71-3064415 (direct)
The Epidemiology, Genetics and Clinical Outcomes (ECO) panel is the newest subgroup of the SIOP RTSG and has been meeting (on-line) since April 2021. It has multi-disciplinary membership, including epidemiology, clinical genetics, biologists, statisticians and parent/survivor representation and wide geographical representation.

The ECO panel was formed to provide leadership in planning and conducting research in the domains of epidemiology, genetics and outcomes research. Our specific focus is to undertake studies that ‘add value’ to the data already held by the SIOP RTSG and to understand variations in populations and healthcare systems.

Our Aims fall into five main categories:

1. To perform hypothesis-driven descriptive analyses of SIOP RTSG datasets to address clinical, genetic and epidemiological questions beyond the main clinical study endpoints
2. To promote joint research with epidemiological researchers and population-based cancer registries to develop novel approaches to assessment of long term morbidity and outcomes in SIOP RTSG trial and study patients e.g. through data linkage
3. To identify common data items and patient/tumour cohorts for comparative analyses with COG and other study groups and data initiatives (HARMONICA, NCI ‘Data Commons’)
4. To align our work with research and quality improvement efforts that use routine healthcare data
5. To involve parents and survivors in our work

For example, we are planning to use the new data items collected at registration on how each new case of childhood renal tumour comes to medical attention to see if there is variation in ‘routes to diagnosis’ across countries participating in UMBRELLA and if this influences stage at diagnosis and outcomes. The UMBRELLA study provides the first opportunity to look at this important aspect of early diagnosis in a systematic way.

There is natural overlap with the subject-specific discipline panels (surgery, radiology, radiotherapy, pathology, biology) and the clinical sub-committees. Our panel membership provides links to each of these and we will work closely with their chairs to maximise efficiency in defining, preparing and cleaning datasets that can be used for multiple projects.

The panel is preparing a work program of projects to be conducted in 2022, once the consolidated SIOP-RTSG study database is ready. Expressions of interest in joining the panel or suggestions for analyses are welcomed. Please contact k.pritchard-jones@ucl.ac.uk

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YI: Young Investigator
Information about the Association

By Marry van den Heuvel-Eibrink and Norbert Graf

In the 50th Anniversary year, the SIOP-RTSG group became a legal entity by establishing the SIOP-RTSG Association. This special, official event took place “in” the notary’s office in Amsterdam, by Zoom, (because of the COVID-19 situation) on the 16th of June 2021, in the presence of all founders. The legal entity allows the group to build up a structure with official Membership, to apply for grants, and to participate as a formal partner, in international collaboration, as documented in the bylaws and the statutes. The Association is grateful for the permission to carry the name SIOP, and for the financial support of the Princess Maxima Center, that made this process and the establishment possible. Calls for membership will be sent out before Christmas 2021. Further furnishing the structure of the group and voting for board positions will take place during the first half of 2022. The General Assembly meeting will be held during the annual scientific meeting in June 2022.

We hope that many of you will apply for membership. It is our conviction that the Association is a big step forward to even better serve patients with kidney tumours and their families.
Young SIOPE is a community for young members of SIOP Europe. It aims to facilitate involvement of SIOPE’s youngest members in research, development, and education. With the Early Career Clinical Trial Group Involvement (ECCTGI) Mentorship Program, Young SIOPE aims to provide the opportunity for young investigators (YIs) to become engaged in the European Clinical Trial Groups (ECTG). By actively contributing to projects and coached by a senior mentor, YIs will be integrated among leading experts and get the opportunity to growth as active members of the group.

In 2021, SIOP-RTSG has officially formed a liaison with Young SIOPE to coordinate the involvement of YIs within RTSG. Christa König serves as coordinator on behalf of YIs, supported by Filippo Spreafico and Jesper Brok, acting as RTSG liaisons. Together we started to develop the process of such involvement.

YIs can still be identified through different sources and collaborations, but their applications should now all be collected centrally by the YI-RTSG coordinator. Exploration of goals and interests of an applicant will allow to identify a suitable mentor within the different panels and subcommittees of RTSG. Furthermore, if a YI is searching for a project within the North American group, we are collaborating with the COG young oncologist liaison, potentially initiating trans-Atlantic research. Formalizing the selection process will increase the likelihood for those YIs working in smaller centres, or from countries with limited connection with the RTSG. Since SIOP RTSG is a wide cooperation far beyond Europe, applicants can be from all over the world and pursue any occupation working with renal tumours in paediatrics. They should be enthusiastic, keen to get involved and interested in a long-term commitment.

Until now, the first call has been shared within the paediatric oncology community and eight candidates had submitted their applications. They participated in a Zoom interview and it was exhilarant to meet all these young and motivated colleagues from different countries and with different backgrounds. Currently we are working on the identification mutual interest and a fruitful way to match them with suitable mentors. We are convinced that this collaboration will be very inspiring for both parties, especially when a YI can work on and promote a specific project.
Some participating countries

Denmark

By Jesper Brok

After hosting the RTSG-SIOP meeting in 2018 Denmark joined the UMBRELLA protocol approximately one year later in December 2019. We are a rather small country with a population of nearly 6 million and expect to see 6-8 renal tumours yearly. Since opening the UMBRELLA we have enrolled 15 patients. As we were not able to join the previous RTSG-SIOP-2001 protocol it is a privilege to contribute and collaborate within the new protocol.

Denmark has 4 departments that treat renal tumours that are placed in Aalborg, Odense, Aarhus, and Copenhagen. Surgery is performed in Odense and Copenhagen whereas proton beam therapy is situated in Aarhus. All upcoming new patients are planned to be discussed at the recently ignited national MDTs. Within the Nordic countries pathology for all patients is smoothly reviewed by Ellen D’Hooghe in Oslo that usually provide feedback within a week! Likewise, David Gisselsson in Lund, Sweden performs exhaustive molecular analyses of multiple tumour samples required for the main molecular analyses eg, 1q gain. Central radiology is kindly conducted by Kristina Vult von Steyern also from Lund. Central radiology is still suboptimal performed via CD shipping of scans. In the nearest future we hope to set up an adequate imaging platform that are easily accessible for all. We aim to explore for and reveal cancer predisposition and therefore all renal tumour patients are offered germline whole genome sequencing. Unfortunately, we are not able to perform urine collection as the required information needed for ethical approval was not fully clear for this research aspect when the protocol was submitted and approved. We are aiming to improve add this in the future.

At the recent national solid committee meeting, we agreed to participate in the new Wilms tumour stage IV randomised trial with support from our new national clinical research unit. Although we only have ~1/year with metastatic disease and the ‘paper’-work is considerable but we find it important to participate if a carefully planned protocol is available. Finally, we are all looking forward to meeting our colleagues live at the next RTSG-SIOP meeting spring 2022.

On behalf of
Karin Bækgård (Aarhus), Eckhard Schomerus (Odense), Steen Rosthøj (Aalborg) and Jesper Brok (Copenhagen)
France

By Arnauld Verschuur, Pediatric Oncologist, National Coordinator for Pediatric Renal Tumours
Department of Pediatric Hematology, Oncology and Immunology, La Timone Hospital, Assistance Publique-Hôpitaux de Marseille

La Timone Hospital is one of the 5 University Hospitals in Marseille that are all integrated into a consortium called Assistance Publique – Hopitaux de Marseille (APHM). This publicly funded consortium provides second-line medical care to a majority of the inhabitants of the Aix-Marseille metropole, the second largest metropole in France. Other private-public hospitals provide second-line care. Besides, the APHM provides third-line medical care in a vast field of specialties for the South-Eastern part of France (Région Sud).

La Timone Hospital has a separate though integrated Children’s Hospital, where all pediatric subspecialties are represented (including PICU) that provide all types of (medical) care and follow-up.

La Timone hospital has a reference center in Pediatric Hematology, Oncology and Immunology. The care of children in this reference center is integrated into a Région Sud/Corsica regional hematology and pediatric oncology care network (REHOP). The management of childhood cancers is organized on an inter-regional scale (Languedoc-Roussillon – Région Sud – Corsica). A multidisciplinary team dedicated to pediatric renal tumors has been established and consists of pediatric oncologists, radiologists, pediatric surgeons, pathologists, biologists and radiation oncologists, as well as non-medical care-providers.

The APHM is the national coordinating center for the SIOP-RTSG 2016 UMBRELLA protocol. As such the APHM acts as a national delegated sponsor and is responsible for the coordination of the multicenter collaboration in the field of pediatric renal tumors in France. SIOP-RTGS Umbrella protocol was opened in September 2019 in Marseille and in 2020 in the other 28 French centers providing care to children with pediatric solid tumours.

All centers collaborate in the national network of pediatric hematology-oncology-immunology called SFCE (Société Française de Lutte contre le Cancer de l’Enfant et de l’Adolescent).

A specific committee exists within the SFCE for all aspects of care and research in the field of pediatric renal tumours, led by Hélène SUDOUR-BONNANGE, Estelle THEBAUD and Arnauld VERSCHUUR.
At present, 173 pediatric patients with renal tumor have been enrolled in the SIOP-RTSG UMBRELLA study in France (of which 6 patients were relapses, 8 patients had a bilateral form, 22 with presumed metastases, 15 patients had direct surgery).

Centralised radiological review is organised on an inter-regional basis by Dr Hervé BRISSE (national reference radiologist) and the national coordinator, designating a pair of referent radiologists for each region in 7 expert centers (Marseille, Institut Curie, Toulouse, Rennes, Clermont-Ferrand, Strasbourg and Lille) of the French Society of Pediatric Imaging (SFIPP) according to the geographical distribution of the centers in France. In the same way, the central pathology review has been divided into 2 zones (North and South), and the review is carried out by a reference review groups of 5 pathologists specialized in renal tumors of children with Prof Aurore COULOMB-L’Herminie being the national reference pathologist.

In terms of biology research, the SFCE committee on pediatric renal tumours decided to focus on biobanking of multiple samples of the nephrectomy specimen ± relapses to contribute to the primary objective of SIOP RTSG 2016 UMBRELLA being the copy number alterations in Wilms tumor (and other biomarkers), as well as the prospective analysis of blastemal residual volume. Moreover, biobanking is performed for future centralized analysis of circulating tumour DNA under the supervision of Gudrun SCHLEIERMACHER (Institut Curie).

The APHM will also be national coordinator for France for the randomized clinical trial “SIOP 2017 RANDOMET” for pediatric patients with metastatic renal tumours (Principal Investigators Rhoikos FURTWANGLER and Arnauld VERSCHUUR).

A phase II clinical trial “Metro-WILMS” is in preparation for patients with second relapses of nephroblastoma with Hélène SUDOUR-BONNANGE and Arnauld VERSCHUUR as Principal Investigators. The Centre Oscar Lambret (Lille) will be the national sponsor for this national multicenter trial that will propose a metronomic multi-drug regimen for these patients.
The Swiss Paediatric Oncology Group (SPOG) is an association whose primary aim is to promote patient-oriented cancer research in the field of paediatric oncology. Through participation in cooperative and predominantly international studies, we want to ensure the best possible treatment for children and adolescents with cancer in Switzerland.

The SPOG coordinating center is located in Bern and responsible for the regulatory coordination and quality management of the SIOP-RTSG UMBRELLA protocol. Paediatric patients with renal tumours are treated at one of the paediatric oncology centres in Switzerland, all of which being members of the SPOG network and participating in the SIOP-RTSG UMBRELLA protocol. They are located at the university hospitals in Bern, Basel, Zurich, Lausanne and Geneva and in the children’s hospitals of St. Gallen, Lucerne, Aarau and Bellinzona.

The University Hospital in Bern is the lead-centre for the SIOP-RTSG UMBRELLA protocol. Together with the University Children’s Hospital in Zurich, the University Hospital Bern shares the responsibility as national reference centre for renal tumour radiology, surgery, pathology, biology and radiotherapy. To guarantee high-quality patient care, a multidisciplinary team of experts discusses all Swiss cases at weekly tumour boards either at the University Hospital Bern or the University Children’s Hospital Zurich.

The SIOP-RTSG UMBRELLA protocol was opened in Switzerland in early March 2020. Recruitment is ongoing at all nine SPOG centres and 23 paediatric patients have been enrolled until the end of October 2021.
Austria
By Leo Kager

Since October 1988 paediatric patients with renal tumours in Austria are recruited into international trials. The first investigation was the Austrian–Hungarian Wilms Tumour Study 1989 (AHWTS-89, N=63 patients). In the AHWTS-89, patients with stage IV disease received upfront Carboplatin. Since June 1994, patients are recruited into the SIOP/GPOH trials (SIOP 93-01/GPOH, N=85 patients and SIOP-2001/GPOH trial and registry, N=247 patients). The SIOP-RTSG 2016 Umbrella study was initiated at the St. Anna Children’s Hospital in Vienna on June 6th, 2021 (NC: Prof. Dr. Leo Kager), and the first patient was enrolled in July 2021. Five Austrian paediatric oncology centres will participate: The St. Anna Children’s Hospital (Medical University Vienna) and the Paediatric Oncology Departments at the University Hospitals in Graz, Innsbruck, Linz and Salzburg. Tumour, blood and urine banking will be performed in the biobank of the St. Anna Children’s Cancer Research Institute (CCRI, www.ccri.at). A national weekly virtual tumour board for different tumour entities is already established. The St. Anna Children’s Hospital and the Medical University Vienna provide national reference radiology (Dr. Karoly Lakatos), -pathology (Prof. Dr. Gabriele Amann), -surgery (Prof. Dr. Martin Metzelder) and -radiotherapy (Prof. Dr. Karin Dieckman). Austria will also participate in the SIOP Randomet 2017 trial (NC: Dr. Waltraud Friesenbichler). Recent publications from the Austrian SIOP-RTSG focused on 13-cis retinoic acid therapy in patients with nephroblastomatosis, clear cell sarcoma of the kidney, and on the immunological landscape of Wilms tumors. We are excited to participate in the SIOP-RTSG Umbrella and Randomet trials, which in the long-term run will help to further improve outcomes in patients with renal tumours.

Literature
Access to the SIOP 2021 Virtual Congress
https://siop-congress.org/

The virtual platform will be accessible from October 21, 2021 at 06:00 AM EDT (Eastern Daylight Time, UTC -4) until January 24, 2022.

SIOP Congress in Barcelona, 2022
https://2022.siop-congress.org/

Hopefully this congress will take place in presence! Follow: https://2022.siop-congress.org/

SAVE THE DATE
September 28 - October 1, 2022
See you in Barcelona, Spain
The SIOP Europe Annual Meeting is coming back in a **physical format** and will take place on **21-25 March 2022 in Valencia, Spain.** The Annual Meeting will once again be held in partnership with CCI Europe, who will be holding their **12th CCI Europe Conference.** This ensures the representation and participation of childhood cancer parents and survivors and provides exceptional possibilities for collaboration across all stakeholders within the paediatric oncology community. Please keep updated: [www.siopeurope.eu](https://www.siopeurope.eu)

**SIOP-RTSG Meeting, Sevilla, Spain, June 26-28, 2022**  
*By Gema Lucía Ramírez Villar*

There are two possibilities for the meeting at the Virgen del Rocío University Hospital. The exact Venue will be announced in time.


This venue has a capacity for 150 people and possibilities for smaller rooms for parallel sessions.
The second venue is the Government building ("aula magna")

This venue has a capacity for 240 people and possibilities for smaller rooms for parallel sessions

Both buildings are included within the complex that houses the Virgen del Rocio University Hospital

The following Hotels are nearby:


Sevilla (SVQ) has a mid-sized airport in Spain: [https://www.aena.es/en/seville.html](https://www.aena.es/en/seville.html)

Last but not least: There are too many things to do after work in Sevilla. Here are some examples:

- [https://www.tripadvisor.com/Attractions-g187443-Activities-Seville_Province_of_Seville_Andalucia.html](https://www.tripadvisor.com/Attractions-g187443-Activities-Seville_Province_of_Seville_Andalucia.html)
11th International Paediatric Renal Tumour Biology Conference, Marseille, 7th – 9th of September 2022

Local host/organizer: Arnauld Verschuur, Marseille
Scientific committee: Sam Behjati, Jesper Brok, Jarno Drost, Conrad Fernandez, James Geller, Manfred Gessler, Vicky Huff, Elizabeth Mullen, Daniela Perotti

PROGRAM (topics covered by invited speakers and selected from abstracts)

Pre-meeting: Biology of renal tumors for clinicians
- Pre-meeting for clinicians to introduce them to molecular genetics (explain techniques and their pitfalls or limitations; biobanking needs)

Advancing diagnosis and treatment of renal tumors – why work on Wilms tumor
- History of Wilms tumor research, Harmonica to link transatlantic RTSG/COG efforts, statement by patient advocacy groups

Keynote: Molecular pathways guiding normal kidney development
- Molecular and cellular basis of nephrogenesis and its detour to oncogenesis (Nils Lindström, USC)

Molecular basis of Wilms tumor
- Novel driver candidates, mutation screening, tumor evolution, tumor heterogeneity, nephrogenic rests, predisposition syndromes
- Drivers of tumor initiation and evolution, nephrogenic rests (Sam Behjati, Wellcome Sanger Centre, UK)

Patterns and diagnostics
- Results from 1q, LOH and TP53 screening, methylation analysis, miRNA expression, liquid biopsy: mutation & CNV screening

Models for functional understanding and drug testing
- Cell lines, 3D cultures, PDX, mouse models, single cell analyses, interface with developmental pathways, drug screening

Non-Wilms tumors
- CMN, CCSK, MRTK, RCC and others

Clinical/Translational aspects
- Familial and bilateral tumors, relapse, new drugs, checkpoints in renal tumors, epidemiology

Further topics to consider / upcoming research options
- New developments from submitted abstracts

Final session: round table "The future of renal tumors, how do we move forward"
- Clinicians, biologists and patient advocacy groups
## Publications

### 2021

1. **Ovidio Jiménez Martin, Andreas Schlosser, Rhoikos Furtwängler, Jenny Wegert, Manfred Gessler**  
   MYCN and MAX alterations in Wilms tumor and identification of novel N-MYC interaction partners as biomarker candidates.  

2. **Nils Welter, Angelo Wagner, Rhoikos Furtwängler, Patrick Melchior, Leo Kager, Christian Vokuhl, Jens-Peter Schenk, Clemens Magnus Meier, Stefan Siemer, Manfred Gessler, Norbert Graf**  
   Characteristics of Nephroblastoma/Nephroblastomatosis in Children with a Clinically Reported Underlying Malformation or Cancer Predisposition Syndrome.  
   Cancers 13 (19), 2021; doi: 10.3390/cancers13195016. – Abstract

   Fifty years of clinical and research studies for childhood renal tumors within the International Society of Pediatric Oncology (SIOP).  

   Interobserver variability between experienced and inexperienced observers in the histopathological analysis of Wilms tumors: a pilot study for future algorithmic approach.  

   MRI-characteristics of Pediatric Renal Tumors: a SIOP-RTSG Radiology panel Delphi Study.  
   Journal of Magnetic Resonance Imaging, first published 6 August 2021; doi: 10.1002/jmri.27878. – Abstract

6. **Gordan M Vujani, Ellen D’Hooghe, Christian Vokuhl, Paola Collini**  
   Dataset for the reporting of nephrectomy specimens for Wilms’ tumour treated with preoperative chemotherapy: recommendations from the International Society of Paediatric Oncology Renal Tumour Study Group.  
   Histopathology 2021 doi: 10.1111/his.14394. – Abstract

   Prognostic factors for Wilms Tumor recurrence: a review of the literature.  
   Cancers 13 3142, 2021; doi: 10.3390/cancers13133142. – Abstract

   Bildgebung renaler Tumoren im Kindesalter.  
   Radiologe, 2021; doi: 10.1007/s00117-021-00864-w. – Abstract

   Wilms tumor surveillance in at-risk children: Literature review and recommendations from the SIOP-Europe Host Genome Working Group and SIOP Renal Tumour Study Group.  
   European Journal of Cancer 153 (2021) 51e63; doi: 10.1016/j.ejca.2021.05.014. – Abstract

10. **Gordan Vujanic, Ellen D’Hooghe, Norbert Graf, Christian Vokuhl, Reem Al-Saadi, Tanzina Chowdhury, Kathy Pritchard-Jones, Rhoikos Furtwaengler**  
    Prognostic significance of histopathological response to preoperative chemotherapy in unilateral Wilms Tumor: An analysis of 899 patients treated on the SIOP WT 2001 protocol in the UK CCLG and GPOH studies.  
    Int J Cancer, 2021; doi: 10.1002/ijc.33707. – Abstract
   Comparative analysis of the clinical characteristics and outcomes of patients with Wilms tumor in the United Kingdom and Japan.

   Estimated clinical benefit of combining highly conformal target volumes with Volumetric-Modulated Arc Therapy (VMAT) versus conventional flank irradiation in pediatric renal tumors.

13. D’Hooghe E, Vujanic GM
   Metanephric stromal tumor

   Locoregional control using highly conformal flank target volumes and volumetric-modulated arc therapy in pediatric renal tumors: Results from the Dutch national cohort.

   Wilms tumor

16. Andreas M. Hötker, Yousef Mazaheri, André Lollert, Jens-Peter Schenk, Junting Zheng, Oguz Akin, Norbert Graf, Gundula Staatz
   Assessment of Response to Neoadjuvant Chemotherapy in Nephroblastoma
   Abdominal Radiology 2021; DOI: 10.1007/s00261-021-03032-9 -> Abstract

   Inter-clinician delineation variation for a new highly-conformal flank target volume in children with renal tumors: A SIOP-Renal Tumor Study Group international multicenter exercise

   Clinical and Molecular Characteristics and Outcome of Cystic Partially Differentiated Nephroblastoma and Cystic Nephroma: A Narrative Review of the Literature
   Cancers 2021, 13, 997; DOI: 10.3390/cancers13050997 -> Abstract

   Outcome of stage IV completely necrotic Wilms tumour and local stage III treated according to the SIOP-2001 protocol
   Cancers 2021, 13(5), 976; DOI: 10.3390/cancers13050976 -> Abstract

   TRIM28 variants and Wilms’ tumour predisposition
   J Pathology 2021; DOI: 10.1002/path.5639 -> Abstract

   Clinical characteristics and outcome of children with WAGR syndrome and Wilms tumor and/or nephroblastomatosis: 30-year SIOP-RTSG experience
   Cancer 127:628-638, 2021; DOI: 10.1002/cncr.33304 -> Abstract
Characteristics and outcome of Pediatric Renal Cell Carcinoma patients registered in the International Society of Pediatric Oncology (SIOP) 93-01, 2001, and UK-IMPORT database: A report of the SIOP-Renal Tumor Study Group
Int J Cancer 2021; DOI: 10.1002/ijc.33476 - Abstract

23. Waltraud Friesenbichler, Rowitha Lüftinger, Gabriele Kropshofer, Martin Henkel, Gabriele Amann, Rhoikos Furtwängler, Norbert Graf, Leo Kager
Clear cell sarcoma of the kidney in Austrian children: Long-term survival after relapse
Ped Blood & Cancer, 2021; DOI: 10.1002/pbc.28860 - Abstract

24. Marie V. Nelson, Marry M. van den Heuvel-Eibrink, Norbert Graf, Jeffrey S. Dome
New approaches to risk stratification for Wilms tumor
Curr Opin Pediatr 2021, 32:000–000; DOI:10.1097/MOP.0000000000000988 - Abstract

Unmet needs for relapsed or refractory Wilms tumour: mapping the molecular features, exploring organoids and designing early phase trials. A collaborative SIOP-RTSG, COG, & ITCC session at the 1st SIOPE meeting

The contribution of surgical clips for optimizing highly-conformal image-guided flank irradiation in pediatric renal tumors: a single center experience

Our Website
Please visit our website. Members of SIOP-RTSG can create an account for the Intranet, where the UMBRELLA protocol, CRFs and other news are shared. We are updating the content regularly.
### Upcoming Meetings

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<td>Valencia, Spain</td>
<td>3rd Annual SIOP Europe Meeting</td>
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<td>5th to 8th of April 2022</td>
<td>Minneapolis, MN, United States</td>
<td>COG Spring Group Meeting (invitation only)</td>
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<td>7th to 9th of September 2022</td>
<td>Marseille, France</td>
<td>12th Int. Pediatric Renal Tumour Biology Conference</td>
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<td>20th to 23rd of September 2022</td>
<td>New Orleans, LA, United States</td>
<td>COG Fall Group Meeting (invitation only)</td>
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<td>28th September to 1st October 2022</td>
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