Newsletter

SIOP Renal Tumour Study Group

Issue 9 2023

Content

Editorial

Dear Colleagues and friends,

It is our pleasure to provide our 9th newsletter of SIOP-RTSG at the end of 2023. Our group was again very active and productive. The Association is running smoothly, and the number of members is increasing. We had a wonderful consortium meeting in June in Wroclaw and presented SIOP-RTSG also at the SIOP Europe meeting in Valencia by holding an educational session with more than 150 participants. The collaboration with COG via Harmonica is a remarkable pillar already with the goal to cure every child with a kidney tumour by enhancing basic research and running clinical trials. This international cooperation is important due to the rarity of kidney tumours and specific subtypes in children. Only by increasing the numbers of patients, new insights in these tumours can be achieved. In a combined effort a Supplemental Issue with an Editorial and 10 Renal Tumour Papers *was published in Pediatric Blood & Cancer giving the state of the art in childhood renal tumours.*

We are looking forward for 2024. You will find a basket of different meetings and conferences. A 2024 Annual meeting of the RTSG will take place, this time in Porto, Portugal, hopefully together with all of you. The 12th International Renal Tumour Biology Conference is scheduled in New York, in June, where recent advances in basic research of renal tumours of childhood will be presented and discussed. At the SIOP congress in Hawaii renal tumours will be a major topic. Therefore, not only Hawaii but also the sessions about renal tumours should stimulate you to attend.

At the end of the year, we would like to thank you all for supporting SIOP-RTSG. It includes all people caring for children with kidney cancers but also for their families and patients allowing us to use their biomaterial and data. In this sense, we wish you all a Merry Christmas and a happy, fruitful, and healthy 2024!

Norbert Graf

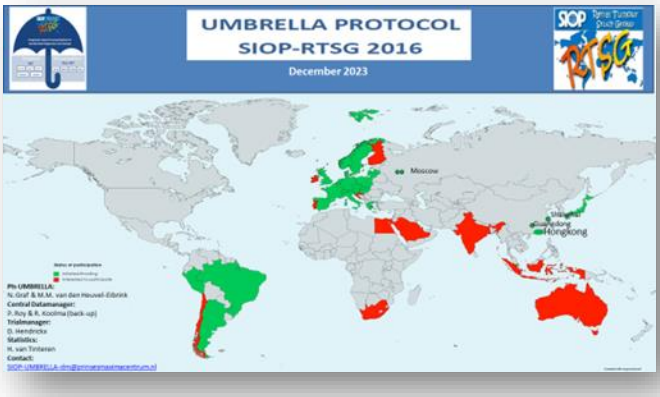
Gordan Vujanic

Nils Welter

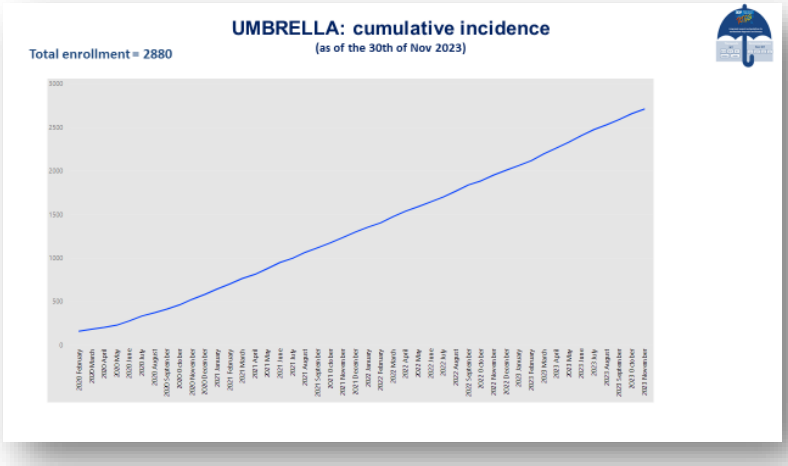
UMBRELLA

By Norbert Graf and Marry M. van den Heuvel-Eibrink

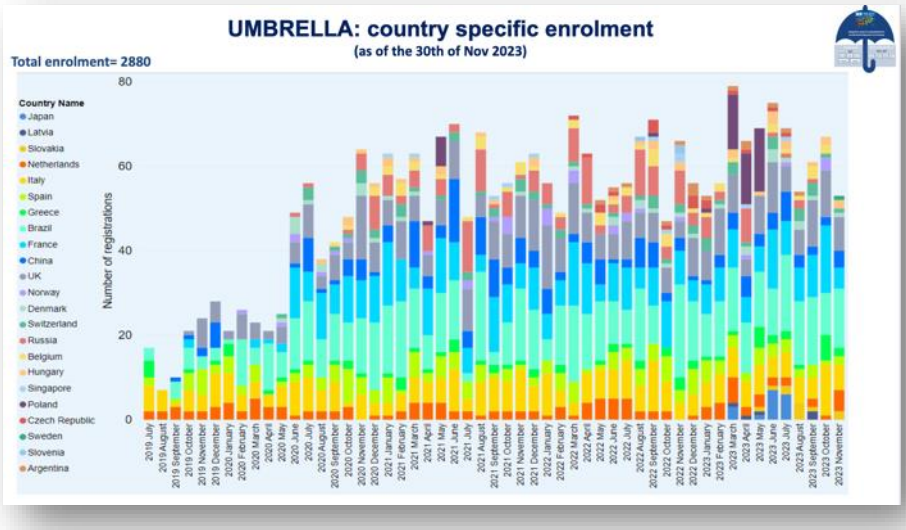
Since the start of the UMBRELLA protocol in 2019 the UMBRELLA study is run ning very well. Since that time 30 countries and nearly 3000 patients have been registered from 26 countries on 3 continents (Asia, South America, and Europe).



Further countries are currently applied to get involved in UMBRELLA. In this process a National coordinator is responsible to fulfil the regulatory requirements of participation. This needs ethical approval, including a translation of the informed consents in the own language, signing of a sponsor contract with the Saarland University (Sponsor) and getting access to ALEA after training and an initiation visit (videoconference). For access to ALEA all reference centres within the country need to be known. The National coordinator needs to initiate all participating local hospitals within the country.



The datacentre is currently in the process, with the help of all National coordinators, of completing all data (including 1q gain data), with the aim to finalize the analyses of the primary study question in 2 years' time.



News from SIOP Randomet 2017

By Arnauld Verschuur and Rhoikos Furtwängler

The SIOP Randomet 2017 study has been initiated in eight countries so far, including Germany, France, Belgium, Switzerland, and Austria. In 2023, Czech Republic, Denmark and the Netherlands joined too, and the first Danish patient has already been included! In these countries, a total of 78 centres are currently open for the study and are recruiting patients (GER: 43, FR: 10, CH: 9, AUS: 5, BEL: 7, CZ: 0, DEN: 3, NL: 1)

The National Coordinating Centres in Spain, Italy, Poland, and Brazil are currently in the process of submitting the protocol to the Competent Authorities and are expected to be initiated in 2024. The transfer of the trial to CTIS, has to take place before and is planned for Q2. Furthermore, we are on the way to include further interested countries such as, Hungary and Greece as soon as possible. The remaining envisaged countries are searching for national funding and/or are preparing submission to the various (as per country) required steps, such as Research Councils, Competent Authorities, Ethical Committee. These subsequent steps are obviously time-consuming for the NCCs as well as the coordinating team of the RANDOMET study and the data management teams in Utrecht and Homburg.

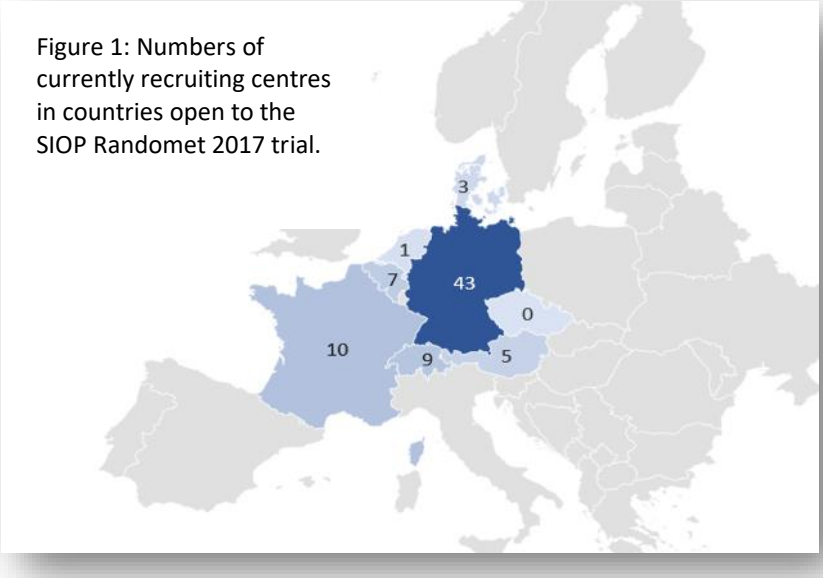


Figure 1: Numbers of currently recruiting centres in countries open to the SIOP Randomet 2017 trial.

Since the start of the study in 2021, 28 patients with stage IV renal tumours from four European countries have been enrolled in the Randomet study, including 19 patients from Germany, six from France, two from Switzerland and one patient from Belgium. 14 patients were randomized in each treatment arm (VAD and VCE). Two high risk histology patients died so far.

An important observation in the two first years of the recruiting phase is a so far high rate of screening failures. In Germany 21 of 40 patients with stage IV renal tumour who would have been eligible for the trial were not included, resulting in a screening failure rate of 52.5%. Further screening failures occurred in Denmark and Belgium (one patient in each country). The most common reasons were the immediate start of preoperative chemotherapy after diagnosis, the refusal of informed consent by the legal guardians and the fact that the respective site was not yet open for recruitment.

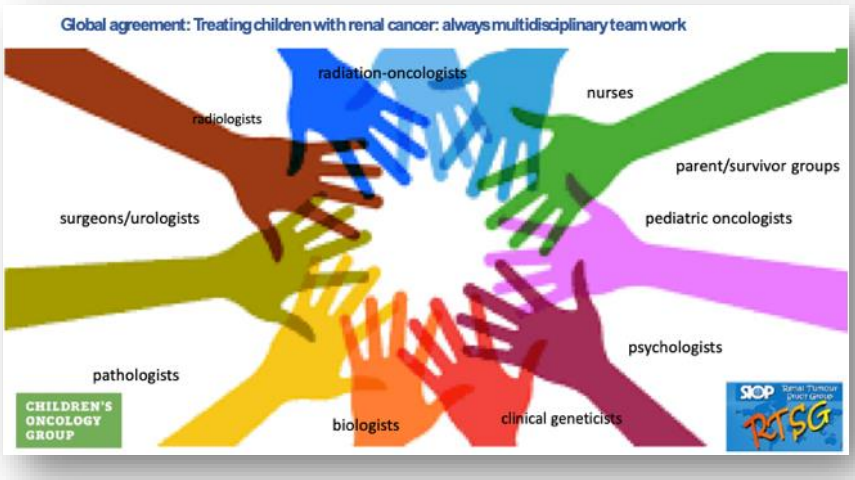
Five patients with a serious adverse event (SAE) were reported in the 2023 annual DSUR report (Developmental Safety Update Report), four of whom were treated in the VAD treatment group. None of the adverse events met the criteria for a suspected unexpected serious adverse reaction after medical evaluation. In summary, the safety profile is consistent with the experience described in the study protocol and there is no change in the risk-benefit ratio or rational.

Overall, we are looking forward speeding up recruitment with the opening of now many of the main centres in continental Europe and are grateful for all your commitment!

HARMONICA

By Marry van den Heuvel-Eibrink and Jim Geller

The HARMONICA (HARMONIZATION and COLLABORATION) initiative has been initiated in 2015, as a collaborative effort between SIOP-RTSG and the Childrens' Oncology Group (COG)-Renal Tumour Committee, with the mission, to enhance survival and to decrease toxicity by joining transatlantic forces, for topics that cannot not be successfully addressed in isolation. This is important as the remaining subgroups of paediatric renal cancer patients has become small, and joined international forces to overcome challenges, are necessary.

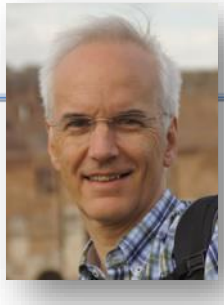


Activities so far, included definitions of endpoints and response criteria, defining the necessary top priority list for pediatric cancer research, common research projects, perspective statements and reviews, collaboration on Innovation, YI twinning and exchange, start of development of Treatment guideline (rare tumors), share data and material, and collaboration on molecular research.

So far, >30 scientific reports have been published, including the May 2023 special issue in PBC, to which 93 authors representing all involved, disciplines, each appearing only once, demonstrating the efficacy of 11 sub-teams within HARMONICA (including YIs and authors from LMICs).

News from the Biology Panel

By Manfred Gessler and Daniela Perotti



Members of the biology panel have been quite active in 2023 and have published a series of interesting papers.

"Hallmark discoveries in the biology of Wilms tumour" curated by Daniela Perotti was published in Nature Reviews Urology and

describes the history of the key advances in the biology of Wilms tumor over 50 years of research, starting from the 'two-hit' model of Alfred Knudson to the most recent findings [1]. The paper covers the genetic insights from the cloning of WT1 to the high-throughput studies that disclosed the genetic landscape of this

disease, the syndromic conditions and familial occurrence, the links of Wilms tumor with kidney development, the efforts made to find and clinically apply prognostic biomarkers, current preclinical models, and the challenges posed by intratumor heterogeneity, tumor recurrence and other areas of active investigation.

Another collaborative effort resulted in a recent review on tumor biology, biomarkers and liquid biopsy that was published in PBC as part of the Harmonica effort to cover all aspects of pediatric renal tumors [2].

Analysis of 126 epithelial Wilms tumors revealed a high rate of TRIM28 loss (44.4 %), and in nearly half of these cases the mutation was present in the germline or as a renal mosaic. This indicates a growing need for genetic counseling in such cases [3]. Surprisingly, these tumors lacked the otherwise common alterations of IGF2/H19 imprinting or additional secondary driver mutations. A high incidence of diverse germline alterations was also reported in a study based on 5-year cohort of Danish Wilms tumor cases [4].

A meticulous analysis of hundreds of tissue sections from a series of 12 diffuse anaplastic Wilms tumors revealed a stepwise transition from stable clones to more proliferating and increasingly anaplastic cells with a high burden 2of double-stranded DNA breaks and copy number alterations [5].

The large-scale project funded by the Little Princes Trust to characterize 1.000 Wilms tumors through omics analyses to create the “Book of Wilms tumors”, is well under way. With genome/exome sequencing as well as RNA-seq accomplished, the data can now be analyzed using various bioinformatics pipelines to identify novel genetic markers to improve diagnosis and therapy and to better define the impact of genetic predisposition. Current efforts are also directed at the analysis of chromosomal gains and losses and their potential to stratify Wilms tumors, which is one of the primary study questions of the UMBRELLA protocol. Based on this enormous amount of genomic data we should be able to come to a final decision on whether we will use the current MLPA testing platform to quantify 1q gain and other CNV markers, or whether an improved and optimized marker panel should be used to screen additional cases that have been collected since.

Efforts to establish organoids as tools to model Wilms tumors and to use them for drug screening have progressed in Utrecht and Würzburg. The Utrecht group of Jarno Drost has been able to establish, characterize and drug-screen 9 relapse WT tumoroid models. Currently these data are being analyzed, and further submissions are still welcome, but full analysis will only start after further funding has been secured.

We are all looking forward to the upcoming 12th International Pediatric Renal Tumor Biology Meeting in New York (June 5-7, 2024), which will surely be the place to learn about the latest and most exciting new developments in pediatric renal tumor biology.

1. Perotti, D., et al., *Hallmark discoveries in the biology of Wilms tumour.* Nat Rev Urol, 2023. Link
2. Walz, A.L., et al., *Tumor biology, biomarkers, and liquid biopsy in pediatric renal tumors.* Pediatr Blood Cancer, 2023. 70 Suppl 2: p. e30130. Link
3. Wegert, J., et al., *TRIM28 inactivation in epithelial nephroblastoma is frequent and often associated with predisposing TRIM28 germline variants.* J Pathol, 2024. **262**(1): p. 10-21. Link
4. Stoltze, U.K., et al., *Germline (epi)genetics reveals high predisposition in females: a 5-year, nationwide, prospective Wilms tumour cohort.* J Med Genet, 2023. **60**(9): p. 842-849. Link
5. Uno, K., et al., *A Gradual Transition Toward Anaplasia in Wilms Tumor Through Tolerance to Genetic Damage.* Mod Pathol, 2023. **37**(1): p. 100382. Link

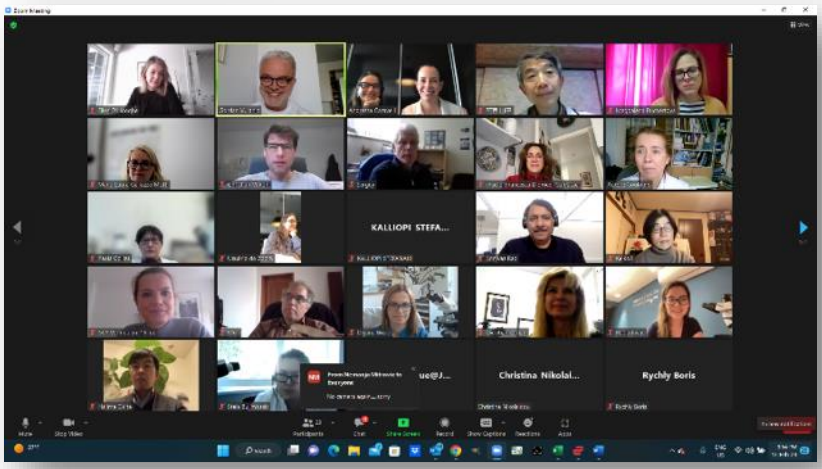
Pathology Panel News

By Gordan Vujanic

The SIOP-RTSG Pathology Panel had a very busy year, trying to catch up with a huge backlog of cases from the pandemic years. We had more meetings than usual, and we combined 'live' and online meetings as follows: Reykjavik (January '23) - ~200 cases (NEPP, GPOH, UK), Brazil (March and April), online – 100 cases, Doha (March) – 350 cases (UK and non-UK cases reviewed by GV), Brazil (June), online – 150 cases, Wroclaw (June) – 150 cases (Polish, GPOH), Nishinomiya City (October) – 50 cases (Japan), and Milano (December) - 150 Italian cases. So, it total, we have reviewed ~1150 cases during this year, which is a truly remarkable achievement, and I am very grateful to all Panel members who contributed to it by attended these meetings and for finding time (and funding for their trips) on the top of their busy regular work. We also invited 30-50 pathologists from the participating countries to attend our online meetings, which they appreciated a lot since it gave them an opportunity to see many more tumours than they would in their practice. We plan to continue combining 'live' and online review meetings because we'll be having more and more cases to review since new countries are still joining the Umbrella study. We were very pleased to meet our colleagues in Japan and review cases together, which gave as an opportunity to establish close links, discuss important pathology issues and fine-tune our criteria.

Reykjavik, January 2023

It is worth mentioning that the International Collaboration on Cancer Reporting (ICCR) recently published the document ("*Paediatric Renal Tumours Histopathology Reporting Guide*"), and some of our members collaborated in its production. The document is intended to help diagnostic pathologists around the world to report renal tumours in a standardised way. Although the idea behind this document is good, the final product is not very helpful. There is an attempt to merge the histological and staging criteria used in SIOP and COG, which are in many instances very different. The resulting scheme may lead to confusion in risk stratification and staging for SIOP cases. Therefore, we recommend that pathologists who deal with paediatric renal tumours treated according to the SIOP-RTSG protocols continue to use only the SIOP-RTSG dataset which is designed specifically for such cases (*Histopathology 2021;79:678-686. doi: 10.1111/his.14394*).



Online review meeting, February 2023

Doha, March 2023

Our members have published several papers on pathology and contributed to other projects (4 as the 1st authors, and 7 as co-authors - please see the list of all publications in this Newsletter).

Wroclaw, June 2023

Nishinomiya City, October 2023

Important publications

1. Vujanić GM, Graf N, D'Hooghe E, Chowdhury T, Vokuhl C, Al-Saadi R, Pritchard-Jones K, Melchior P, Furtwängler R: Outcomes of patients with Wilms' tumour stage III due to positive resection margins only: An analysis of patients treated on the SIOP-WT-2001 protocol in the UK-CCLG and GPOH studies. Int J Cancer. 2023 Apr 15;152(8):1640-1647. doi: 10.1002/ijc.34371.

2. D'Hooghe E, Furtwängler R, Chowdhury T, Vokuhl C, Al-Saadi R, Pritchard-Jones K, Graf N, Vujanić GM: Stage I epithelial or stromal type Wilms tumors are low risk tumors: An analysis of patients treated on the SIOP-WT-2001 protocol in the UK-CCLG and GPOH studies (2001–2020). Cancer 129:1930-1938, 2023: doi:10.1002/cncr.34734
3. Vujanic GM, Galluzzo Mutti L, Popov SD: Renal tumours of childhood: what's new in classification, morphology, molecular findings and prognosis. Diagn Histopath 2023. doi: 10.1016/j.mpdhp.2023.09.003
4. D'Hooghe E, Vujanic GM: Ossifying renal tumour of infancy. PathologyOutlines.com. https://www.pathologyoutlines.com/topic/kidneytumorossifying.html

Milano, December 2023

News from the Radiology Panel

By Jens-Peter Schenk, Hervé Brissé, Annemieke Littooij, Justine van der Beek

The radiology panel is the representative of the radiologists involved in research studies of the SIOP-RTSG association and is responsible for the data collection with radiology forms in the Umbrella protocol and Randomet protocol for stage IV Wilms tumours.

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 and is still proceeding in 2023 and 2024. F2R forms are used in ALEA and OPTIMA platforms. In Germany the MDPE-Server is working since 2022 for all participating German oncology centres and replaced the conventional reference radiology system completely.

Activities:

In continuation of the work of 2022 the panel continued the studies for Non-Wilms Tumours with members of the panel with a high amount of registered Non-WT, e.g. rhabdoid tumours and clear cell sarcomas. The study was organized and finished this year by Justine van der Beek and Annemieke Littooij from the Princess Máxima Center for Paediatric Oncology in Utrecht. Participating countries were, based on long experience with MRI in the national reference radiology program, Germany, Spain, the UK, Italy, and The Netherlands. To be able to use a case report form for tumour characteristics on an international level, an interrater agreement study is currently conducted online with anonymous data of tumours.

Publication:

Van der Beek J et al. Diagnostic MRI characteristics of pediatric Clear Cell Sarcoma of the Kidney and Rhabdoid Tumor of the Kidney: A retrospective multi-center SIOP-RTSG Radiology panel study. Accepted 2023 in EJC Paediatric Oncology.

This study was followed by a study of registered congenital mesoblastic nephromas, CMN with similar data acquisition and method of the study. Evaluated parameters among other parameters are ADC-values and detection of pseudocapsula in these tumours.

Members of the panel are involved in clinical studies of the SIOP-RTSG panels. Head of the panel are Jens-Peter Schenk and Hervé Brissé. Carlo Morosi from Milano (Italy) is representative of our group in imaging questions to tumour relapse. Annemieke Littooij is representative of the group in research activities and Harmonica.

Future projects are considered with AI, e.g. automated round nodule detection in thoracic CT and the use of AI in radiotherapy planning using MR images.

Members of the panel are still active in definition of the patient subgroup for tumour biopsy before chemotherapy.

Regarding 2024, a ESPR collaboration in perspective of Wilms tumour rupture with a publication project in Paediatric Radiology is planned.

News from the Radiotherapy Panel

By Patrick Melchior and Geert Janssens

The radiotherapy panel is the representative of the radiooncologists involved in research studies of SIOP-RTSG and reference radiooncology in the current UMBRELLA registry trial.

In 2023, the radiotherapy panel is continuing its work from 2022 and is involved in further research projects. These projects include international standardization of radiotherapy concepts in kidney tumour, collaboration with the COG (Harmonica), optimizing data collection and retrospective radiation-related analyses based on merged databases of recent SIOP studies (SIOP-2001, 93-01 and SIOP-UMBRELLA) as well as integration of modern irradiation techniques safely into daily radiation practice.

The radiotherapy group is also working on the prospective multicenter observational study, using the QUARTET platform, a Radiation Treatment Quality Assurance, to compare conventional and modern irradiation techniques. The study aims to observe the relevance of target volume reduction concerning long-term local control and toxicity, as well as to avoid significant interobserver target volume and treatment plan variation [1]. New data from France has shown excellent survival outcomes, acceptable toxicity profiles, and a low incidence of local abdominal relapses after irradiation using modern techniques combined with reduced target volume concepts.

Another research project focuses on a new target delineation entitled „**Towards para-aortic lymph node irradiation in Wilms tumors with lymph node involvement only**". This project aims to find evidence for further target volume reduction using a multistep approach, which includes an international Delphi and delineation study, as well as a SIOP-RTSG patient analysis. Additionally, an estimation of the clinical benefit of the new approach will be performed through an *in silico* study. The outcome of this project can serve as a basis for a future prospective international study within the next SIOP-RTSG protocol, ultimately reducing the risk of growth disturbances, functional asplenia and diabetes/metabolic syndrome for a subgroup of patients.

In collaboration with the SIOPEN, the radiotherapy group is working on a review project focusing on '**late toxicity after upper abdominal radiotherapy in pediatric cancer patients**'. The goal is to create a practical review paper on behalf of the SIOP-RTSG/SIOPEN radiotherapy groups, which would be useful for all disciplines involved in the treatment of pediatric renal tumors and neuroblastoma.

Current active SIOP-RTSG core group members of the radiotherapy panel:

Patrick Melchior (Chair, Germany)	Geert Janssens (Co-Chair, The Netherlands)
Christian Rübe (Germany)	Davila Fajardo (The Netherlands)
Daniel Saunders (United Kingdom)	Farid Alam (United Kingdom)
Aymeri Huchet (France)	Xavier Muraciole (France)
Emmanuel Jouglar (France)	Karin Dieckmann (Vienna)

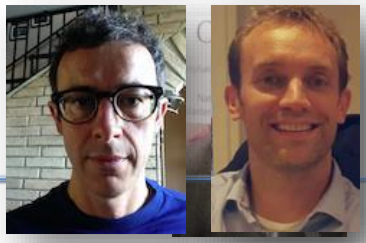
All radiooncologists interested in paediatric renal tumours are very welcome to work with us in the radiotherapy panel of SIOP-RTSG.

References:

1. Janssens GO, Melchior P, Mul J, et al. The SIOP-Renal Tumour Study Group consensus statement on flank target volume delineation for highly conformal radiotherapy. *Lancet Child Adolesc Heal*. 2020;4(11):846-852. doi:10.1016/S2352-4642(20)30183-8
2. Gaelle Le Quellenec et al., Post operative flank irradiation using conformal versus highly conformal radiotherapy techniques for paediatric renaltumours: Results from the French registry PediaRT Pediatr Blood Cancer.2023;70:e30627. doi.org/10.1002/pbc.30627

The Relapse and New Agents

By Filippo Spreafico and Jesper Brok on behalf of all the committee members



The Relapse Committee has actively operated through this year, trying to add pieces to the complex puzzle of the relapsed Wilms world.

We remind us and every member that the first mission of the Relapse and New Agent SIOP RTSG committee and panel, respectively, are to provide the gold standard of treatment to as many paediatric oncology centres as possible, via the RTSG-SIOP collaboration and to initiate basic/clinical research and inspiring new trials with novel drugs.

Through our operative meetings, and with the support of the YIs actively involved, we analysed historical and Umbrella patients with relapsed Wilms tumours in order to accumulate evidence on the current risk stratification (see AA, BB and CC groups) and related treatment options.

Relapse AA group maintains satisfactory EFS rates after relapse, in the range of 70%, let us open the door to less intensive rescue treatment in selected groups of patients. ICE/CyCE treatment regimens are likely the best standard to re-treat patients of the BB group, for whom high-dose melphalan and autologous bone marrow rescue might offer advantage. For the CC group we definitively need novel therapeutics, confirming the poor outcome with the current options of treatment. For this last group of patients, Annelies Mavinkuurve-Groothuis (form PMC) is leading a grant submission to support a phase II trial testing the efficacy of VITB (vincristine/irinotecan/temozolomide/bevacizumab) combination in this group of patients.
Our analysis are also reinforcing that surgery and radiation therapy at relapse might play a role, and thus we need high-quality data to guide next generation of relapse guidelines.

This group has started our brainstorming bringing us to the next generation of SIOP RTSG protocols and studies at relapse.

Ottawa SIOP-meeting 2023

Harmonica working session on relapse Wilms tumour:

Both COG (K Sutton, A Walz and J Brzezinski) and RTSG-SIOP (S van Peer, J van der Beek, and J Brok) each presented 3 relapse cases with either standard risk, high-risk or very high-risk features. The aim was a concise presentation of each case followed by a thorough but informal discussion. Predominantly oncologists but also surgeons and radiotherapists and radiologists participated. Similarities and differences in approaches were revealed from both the COG and RTSG perspective. Interestingly, emerging data indicate that the standard risk patients may have very good outcome whereas the very high-risk still have a poor prognosis. The decision of biopsy vs. surgery (or even no procedure) at relapse is complicated and the timing of surgery and radiotherapy but also the benefit and harms of these interventions in a relapse setting are key challenges. Such aspects were discussed. Additionally, ideas for upcoming relapse treatment modifications and adjacent research were ignited. These aspects will be discussed further at upcoming Harmonica meetings. A similar clinical trans-Atlantic session could easily be repeated in the future.

Thanks to SIOP for providing facilities, the speakers, participants, and J Geller for his energy in co-facilitating the session.

Young investigators of the paediatric oncology community in SIOP-RTSG



By Christa König, Jesper Brok and Filippo Spreafico

SIOP-RTSG initiated the engagement of young investigators in 2021.
We are proud to announce that we now have 20 young colleagues participating in various ways within SIOP-RTSG.

They have diverse backgrounds, including pathology, pediatric oncology, clinical genetics, radiology, or pediatric surgery, and they come from twelve different countries (Croatia, France, Germany, Guatemala, Ireland, Italy, Netherlands, Portugal, Spain, Ukraine, the United Kingdom, and Switzerland). Approximately 2/3 of the young investigators (YIs) are paired with a mentor within SIOP-RTSG and/or a panel/subcommittee. We believe that mentorship is crucial for the successful involvement of young colleagues. When you study the most successful individuals today, from renowned entrepreneurs to your favourite authors or musicians, at some point in their careers, they had someone in their field who was more experienced, guiding them through the intricacies of the business and teaching them what was necessary to succeed. Like in any other field, mentoring in healthcare involves taking someone less experienced under your tutelage and helping them grow. It can be an incredibly rewarding experience for both the mentor and the mentee, but it can also be quite challenging. The idea is to build a mutually beneficial relationship based on respect, trust, and open communication. Only then will both parties be able to get the most out of the experience.

Thus far, the YIs of SIOP-RTSG have worked on various projects, submitted research proposals to the steering committee, presentations at the annual meeting and contributed to publications and parts of the HARMONICA project. We have a connection to the COG Renal Tumor Committee YIs and plan to start regular online meetings and training for YIs. In Wroclaw, the YIs also demonstrated, that they can organize very enjoyable parties.

The feedback regarding the initiative remains very enthusiastic, and SIOP-RTSG members continue to be very open to involving YIs. We will persist in integrating YIs and building the next generation of SIOP-RTSG.

Pictures: Young investigators at the SIOP-RTSG Meeting in Wroclaw

Some participating countries

Belgium

By An Michiels and Heidi Segers

Belgium has a population of 11,5 million people. Approximately 350 children and adolescents between 0-14 years and 150 adolescents between 15-19 years are diagnosed with cancer in Belgium each year of which +/- 20 patients are diagnosed with a renal tumour. Patients with a renal tumour are treated in one of the seven recognised centres for Paediatric Haemato-oncology of which UZ Leuven is one. These 7 centres are united in a national organisation, the Belgian Society for Paediatric Haematology and Oncology (BSPHO). Each hospital has a multidisciplinary team dedicated to paediatric renal tumours with paediatric oncologists, radiologists, urologist surgeons, pathologist, biologist, and radiation oncologists. This multidisciplinary team discusses all new cases.

Belgium has been included in the international collaboration within the Renal Tumour Study group (SIOP-RTSG) for years. International treatment guidelines were followed, and Belgian patients were registered in the SIOP 2001 study. Belgium is participating to the Umbrella study and the Randomet study. At national level, all new renal tumour cases have:

- *central pathology review (pathologist Dr Ronald de Krijger – UMC Utrecht – The Netherlands)*
- *national radiology review (radiologist Prof Dr Luc Breysem – University Hospital Leuven)*
- *national review surgery for bilateral cases (surgeon Prof Dr Maarten Albersen – University Hospital Leuven)*
- *national review radiotherapy (radiotherapist Dr Karen Van Beek - – University Hospital Leuven)*

Difficult cases are discussed at the weekly national tumour board meetings. If necessary international experts are contacted for advice.

The Umbrella study was initiated in Belgium on 16 July 2020. Since then, a total of 52 patients were included. Biobanking of tumour material, blood and urine is centralised in the University Hospital of Leuven to facilitate biological research within this project.

Year	N° of patients
2020	4
2021	17
2022	18
2023	13

The Randomet study was initiated on 09 May 2022 and per year we expect around 2 patients to be included. So far, two patients were already screened for this study. One patient could not be included because of a technical error in the e-CRF. One patient was successfully included.

The Umbrella and Randomet study are supported by the Belgian Society for Paediatric Haematology and Oncology (BSPHO), who coordinated the start-up and is taking care of the project management of these clinical trials. Heidi Segers, Paediatric Haemato-oncologist, is the National Coordinator for Paediatric Renal tumours and National Coordinating Investigator of SIOP Umbrella and Randomet study at the University Hospital of Leuven and An Michiels is the national project manager at BSPHO/University Hospital of Leuven

We are excited to be part of this international collaboration and to participate in the SIOP-RTSG Umbrella and Randomet study, which will help to improve short and long-term outcomes of children with renal tumours.

Brazil: Catching up with history

By Joaquim Caetano de Aguirre and Beatriz Camargo

The Renal Tumor Group in Brazil started in 1986 with the GBTTW (Brazilian Wilms Tumor Study Group). (1, 2) Since then, the Brazilian group has improved significantly in clinical research in renal tumors in Brazil. One of the significant milestones in GBTTW's journey was its involvement in the SIOP-2001 study in 2001, where the group contributed valuable data from 514 patients. (3) In 2016, recognizing the need for a more comprehensive approach, the GBTTW transformed into the Brazilian Renal Tumor Group (GBTR) and initiated a pilot study that included a routine central review of images and pathology. This move marked the group's ambition to participate in the UMBRELLA-SIOP-RTSG initiative.

Since June 2019, GBTR began actively registering cases in UMBRELLA-SIOP-RTSG-2016. Five hundred and seventy-seven cases have been registered so far, indicating a progressive engagement of 49 centers from all 5 regions of Brazil. It is estimated that GBTR now captures 40-50% of all new cases in Brazil, evidence of its influence in the country's pediatric oncology landscape.

The year 2021 was particularly noteworthy for GBTR, as it hosted the annual UMBRELLA meeting in Rio de Janeiro, Brazil. The event witnessed increased registrations (Figure 1), signaling a growing interest and participation in the collaborative efforts on renal tumors. The GBTR's dedication to knowledge sharing and collaboration has made it a pivotal force in shaping pediatric oncology in Brazil. In response to the ever-growing need for real-time discussions, GBTR initiated two weekly virtual meetings in 2021 to discuss all new cases, including carefully reviewing images, staging, and risk group classification. (4)

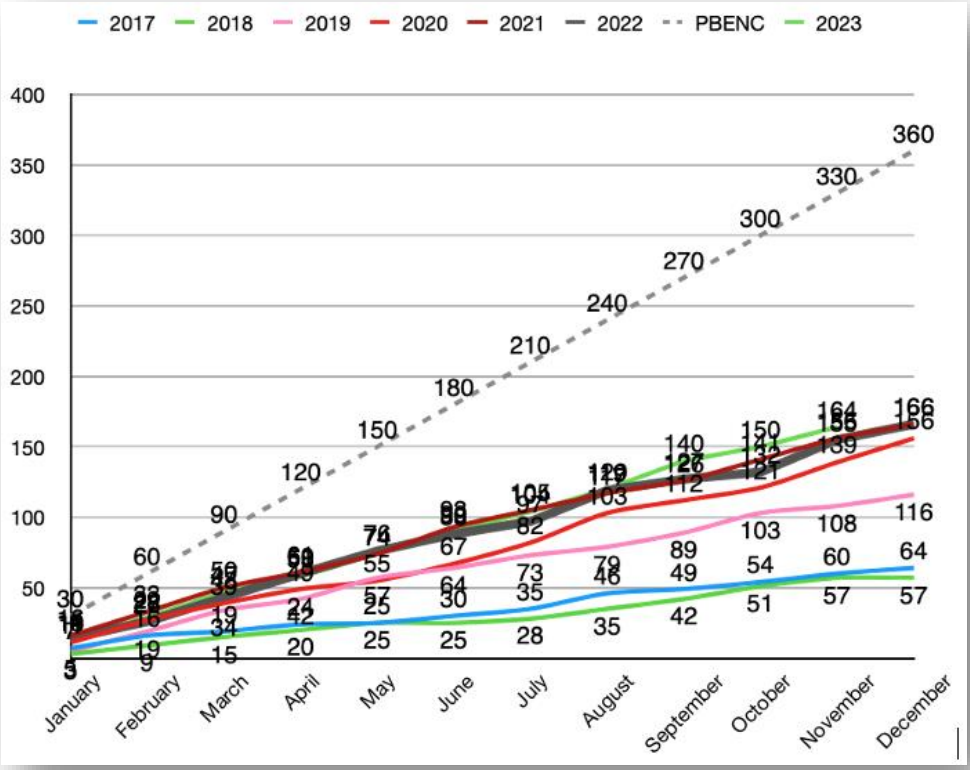


Figure 1: Number of patients registered at GBTR during the last 7 years.
PBENC: Population-based estimated number of cases

During 2023, sixty-nine meetings were conducted via Zoom, averaging six monthly sessions. Each meeting discussed at least four cases, highlighting GBTR's commitment to thoroughly examining the complexities of pediatric renal tumors. The main reason for discussion has been image and pathology review staging. A unique highlight in GBTR's collaborative efforts is the regular engagement with colleagues from the Latin America Pediatric Oncology Group (GALOP).

Once a month, GBTR and GALOP join forces, fostering a sense of unity in the pursuit of excellence in renal tumor research across Latin America. Additionally, GBTR encourages participation in the GALOP- organizing a Renal Tumor Network (GALOP Network). Annual local meetings are being held to update the Brazilian colleagues the participation in UMBRELLA. (Figure 2) Together, we look forward to *catching up* with all the scientific development, building a better future for all children with renal tumors in Brazil and other countries from Latin America.

1. de Camargo B, de Andrea ML, Franco EL. Catching up with history: treatment of Wilms' tumor in a developing country. Med Pediatr Oncol. 1987; 15:270-6.
2. de Camargo B, Franco EL. Single-dose versus fractionated-dose dactinomycin in the treatment of Wilms' tumor. Preliminary results of a clinical trial. The Brazilian Wilms' Tumor Study Group. Cancer. 1991 15;67:2990-6.
3. de Aguirre-Neto JC, de Camargo B, van Tinteren H, et al. International Comparisons of Clinical Demographics and Outcomes in the International Society of Pediatric Oncology Wilms Tumor 2001 Trial and Study. JCO Glob Oncol. 2022; 8:e2100425.
4. de Aguirre-Neto JC, Testes R, Lederman H, de Camargo B. The Impact of Multidisciplinary Meetings on the Diagnosis and Management of Brazilian Patients with Renal Tumors. Supplement: Abstracts from the 55th Congress of the International Society of Paediatric Oncology (SIOP) October 11–14, 2023. S319.

Brasilia 2022

Belo Horizonte 2023

Figure 2 Brazilian Renal Tumor Local Annual Meetings

SIOP-RTSG Annual Meeting
Wroclaw, Poland, June 21-24, 2023

The SIOP-RTSG Annual Meeting was held in Wroclaw, Poland from the 21st to the 24th of June. More than 180 participants from 21 countries from all continents did participate in this excellent "come together" in the wonderful city of Wroclaw.

Updates of the running UMBRELLA study and randomized Randomet trial were presented and discussed. All panels gave an overview of their achievements during the last year and addressed future topics of their groups that will be further discussed during the preparation of an upcoming UMBRELLA study. Young investigators were actively included in the program discussing case reports and presented scientific research questions. For the first time 11 posters were demonstrated and lively discussed.

Slovenia, Lithunia, Japan, Latvia and Argentina as new participating countries gave talks about their situation in treating children with kidney cancers in their countries. Prof Davidoff from St. Jude Children's Research Hospital, USA, gave a lecture about the correlation of tumour shrinkage with histology in bilateral Wilms tumour that was intensively discussed.

A General Assembly for full members of SIOP-RTSG started in the morning of the second day looking back on achievements of the first year of our association and presenting an outlook for the future. Information about important issues for our association including a financial report, fundraising options, international collaboration, and others were discussed with members and suggestions collected from them how to improve SIOP-RTSG over the next few years.

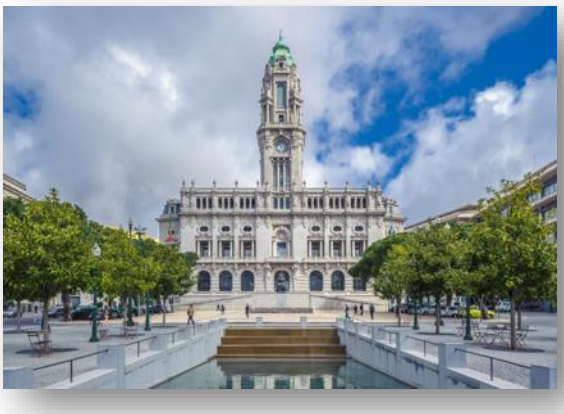
After a lot of work during the meeting we enjoyed a great Dinner and a boat trip in the evenings. On Saturday part of us visited the Castle Książ before we needed to return back to home.

A GREAT THANK to Jan Godzinski and his team for hosting this excellent meeting and the overwhelming hospitality. Now we are looking forward to our next meeting in Porto in 2024.

SIOP-RTSG Annual Meeting
Porto, Portugal, September 16-18, 2024

We are looking forward to seeing you in the wonderful city of Porto for our Annual SIOP-RTSG meeting in September 2024.

Details of the meeting will follow soon and will be send to our members and can be found on our website with information for registration and an agenda with topics of the meeting.

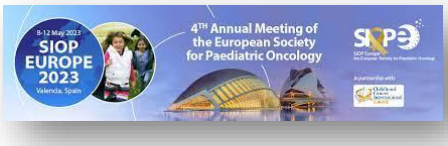


12th International Paediatric Renal Tumour Biology Conference, New York, 6th – 7th of June 2024

Two-years after the successful 11th International Paediatric Renal Tumor Biology Conference in Marseille we will have the next one in New York in June 2024. This combined meeting between SIOP-RTSG and COG will bring all research groups together that are working in the field of childhood renal tumors. We are looking forward meeting you at this exciting event.

SIOP-Europe Annual Meeting in Valencia, Spain, 2023

By Marry M. van den Heuvel-Eibrink



At the SIOPe meeting in Valencia, in May 2023, 70 SIOP-RTSG members were registered as participants. SIOP-RTSG organized an educational meeting.

Presented topics in the Wednesdays Educational SIOP-RTSG meeting were:

- Global Harmonization and collaboration towards enhanced renal tumour cure (M.M. van den Heuvel-Eibrink
- The evolving scene for paediatric renal tumours based on molecular profiling (J. Brok)
- Innovative radiotherapy for renal tumours (P. Melchior)
- Image guided surgery: Innovation for children with renal tumours (J. Godzinski/M. Pachl)
- The role of YIs in SIOP-RTSG: Experts for further progress (C. Koenig)
- The role of patients/parents/survivors' advocacy for paediatric renal cancers (A Polanco)

This educational meeting was attended by 161 participants.

In addition, on the Thursday a joined meeting of SIOP-RTSG was held together with PanCare, where relevant new insights of endocrine sequelae, nephrotoxicity, frailty, fertility, social participation, after paediatric renal cancer (Drs. E. Verwaaijen ,Drs. D. de Winter, Dr. S. Høgsholt, Drs. M. van der Perk), as well as an IGHG (International Guideline Harmonisation Group) guideline for nephrotoxicity surveillance for childhood cancer survivors (Dr. E. Kooijmans) were presented, mainly by young investigators. This joined session was attended by over 200 participants.

SIOP-Europe Annual Meeting in Milano, Italy, 2024

https://siopeurope.eu/

We are delighted to welcome you to the 5th SIOP Europe Annual Meeting which will take place in Milan, Italy on 13-17 May 2024.

This meeting **brings together the diverse stakeholders** involved in facing key issues for children and adolescents with cancer. The SIOP Europe Annual Meeting provides a unique interactive format to discuss the current priorities and needs in the field of childhood cancers. The Annual Meeting is **held in partnership with CCI Europe**, ensuring the representation and participation of childhood cancer parents and survivors.

We hope to see you on **13-17 May 2024 in Milan, Italy** for another memorable SIOP Europe Annual Meeting! Registrations are now open! Please keep updated: **www.siopeurope.eu**

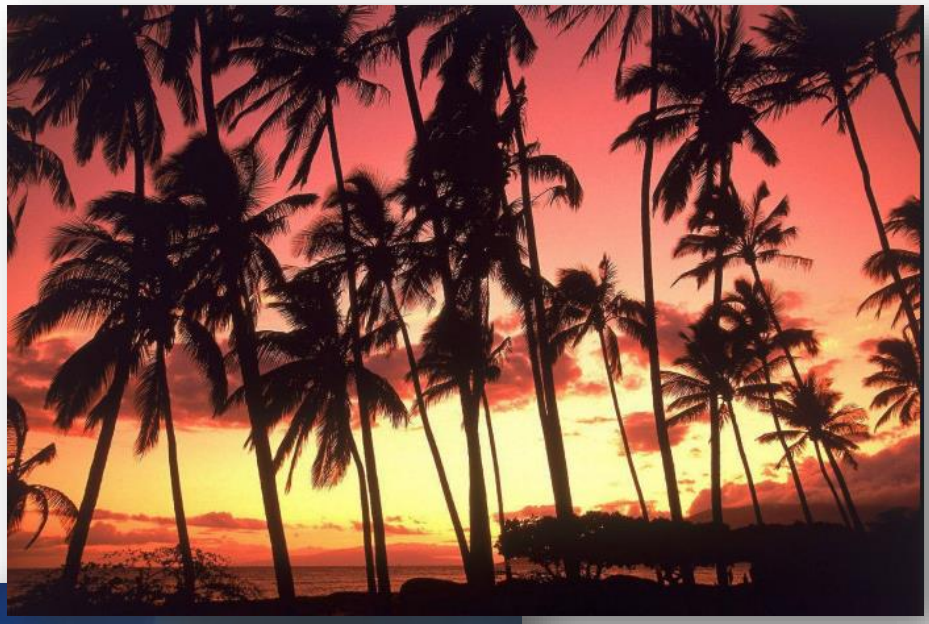
SIOP Congress in Honolulu, Hawaii, USA 2024

https://2024.siop-congress.org/

This congress will take place in presence! Follow: https://siop-congress.org/

Experience 4 outstanding days of cutting-edge science, engaging debates and networking with world-renowned experts at SIOP 2024!

Advance your paediatric oncology career, connect with like-minded people, and contribute to a world where no child should die of cancer!



Publications 2023

1. **Jörg Fuchs, Matthias C Schunn, Jürgen F Schäfer, Martin Ebinger, Norbert Graf, Rhoikos Furtwängler, Steven W Warmann**
   Redo Nephron-sparing surgery in stage V pediatric renal tumors – a report from the SIOP/GPOH Study Group for renal tumors
   Eur J Surg Oncol 50(1):107265, 2024; doi: 10.1016/j.ejso.2023.107265 -> Abstract

2. **Justine N van der Beek, Jens-Peter Schenk, Tom A. Watson, Ana Coma, Carlo Morosi, Norbert Graf, Tanzina Chowdhury, Gema L. Ramírez-Villar, Filippo Spreafico, Kristina Dzhuma, Lidwine B. Mokkink, Ronald R. de Krijger, MarryM. van den Heuvel-Eibrink, Annemieke S. Littooij**
   Diagnostic MRI characteristics of pediatric Clear Cell Sarcoma of the Kidney and Rhabdoid Tumor of the Kidney: A retrospective multi-center SIOP-RTSG Radiology panel study.
   EJC Paediatric Oncology 2023. doi: 10.1016/j.ejcped.2023.100122 ->Abstract

3. **Daniela Perotti, Richard D. Williams, Jenny Wegert, Jack Brzezinski, Mariana Maschietto, Sara Ciceri, David Gisselsson, Samantha Gadd, Amy L. Walz, Rhoikos Furtwangler, Jarno Drost, Reem Al-Saadi, Nicholas Evangeliou, Saskia L. Gooskens, Andrew L. Hong, Andrew J Murphy, Michael V Ortiz, Maureen J. O'Sullivan, Elizabeth A. Mullen, Marry M. van den Heuvel-Eibrink, Conrad V Fernandez, Norbert Graf, Paul E. Grundy, James I. Geller, Jeffrey S. Dome, Elizabeth J. Perlman, Manfred Gessler, Vicki Huff, Kathy Pritchard-Jones**
   Hallmark discoveries in the biology of Wilms tumor and of the other pediatric renal tumors.
   Nature Reviews Urology, 2023. doi: 10.1038/s41585-023-00824-0 ->Abstract

4. **Jenny Wegert, Anne Kristin Fischer, Balazs Palhazi, D. Taryn Treger, Cäcilia Hilgers, Barbara Ziegler, Hyunchul Jung, Eva Jüttner, Andreas Waha, Jörg Fuchs, Steven W. Warmann, Michael C. Frühwald, Jochen Hubertus, Kathy Pritchard-Jones, Norbert Graf, Sam Behjati, Rhoikos Furtwängler, Manfred Gessler, Christian Vokuhl**
   TRIM28 inactivation in epithelial nephroblastoma is frequent and often associated with predisposing TRIM28 germline variants.
   J Pathology, 2023. doi: 10.1002/path.6206 ->Abstract

5. **Vujanic GM, Galluzzo Mutti L, Popov SD**
   Renal tumours of childhood: what's new in classification, morphology, molecular findings and prognosis.
   Diagn Histopath 2023. doi: 10.1016/j.mpdhp.2023.09.003 ->Abstract

6. **Georgios Politis, Stefan Wagenpfeil, Nils Welter, Marvin Mergen, Rhoikos Furtwängler, Norbert Graf**
   An Observational Case-Control Study on Parental Age and Childhood Renal Tumors.
   Cancers (Basel). 202315:5144. doi: 10.3390/cancers15215144 ->Abstract

7. **Avčin SL, Črepinšek K, Jenko Bizjan B, Šket R, Kovač J, Vrhovšek B, Blazina J, Blatnik O, Kordič R, Kitanovski L, Jazbec J, Debeljak M, Tesovnik T**
   Integrative Transcriptomic Profiling of the Wilms Tumor.
   Cancers (Basel). 2023 Jul 28;15(15):3846. doi: 10.3390/cancers15153846. PMID: 37568662; PMCID: PMC10416970 ->Abstract

8. **Prakriti Roy, Sophie E van Peer, Rana Dandis, Catriona Duncan, Joaquim Caetano de Aguirre-Neto, Arnauld Verschuur, Beatriz de Camargo, Henrike E. Karim-Kos, Luna Boschetti, Filippo Spreafico, Gema L. Ramirez-Villar, Norbert Graf, Harm van Tinteren, Kathy Pritchard-Jones, Marry M van den Heuvel-Eibrink**
   Impact of the COVID-19 pandemic on paediatric renal tumour presentation and management, a SIOP Renal Tumour Study Group study.
   Cancer Medicine, 2023; doi: 10.1002/cam4.6358 ->Abstract

9. **Meier Clemens Magnus, Fuchs Jörg, von Schweinitz Dietrich, Stein Raimund, Wagenpfeil Stefan, Kager Leo, Schenk Jens-Peter, Vokuhl Christian, Melchior Patrick, Welter Nils, Furtwängler Rhoikos, Graf Norbert**
   Surgical Factors Influencing Local Relapse and Outcome in the Treatment of Unilateral Nephroblastoma.
   Annals of Surgery 278:e360-e367, 2023; doi: 10.1097/SLA.0000000000005690; ->Abstract

10. **D'Hooghe E, Vujanic GM**
    Ossifying renal tumour of infancy.
    PathologyOutlines.com (2023) website.
    https://www.pathologyoutlines.com/topic/kidneytumorossifying.html; ->Paper

11. **Vujanić GM, Graf N, D'Hooghe E, Chowdhury T, Vokuhl C, Al-Saadi R, Pritchard-Jones K, Melchior P, Furtwängler R**
    Outcomes of patients with Wilms' tumour stage III due to positive resection margins only: An analysis of patients treated on the SIOP-WT-2001 protocol in the UK-CCLG and GPOH studies.
    Int J Cancer. 2023 Apr 15;152(8):1640-1647. Doi: 10.1002/ijc.34371. Epub 2022 Nov 30. PMID: 36444500; ->Abstract

12. 

    Pediatric Renal Tumors – A HARMONICA Initiative
    PBC 70 (S2) 2023 ->A Supplemental Issue with an Editorial and 10 Renal Tumor Papers

13. **Ellen D'Hooghe, Rhoikos Furtwängler, Tanzina Chowdhury, Christian Vokuhl, Reem Al-Saadi, Kathy Pritchard-Jones, Norbert Graf, Gordan M. Vujanić**
    Stage I epithelial or stromal type Wilms tumors are low risk tumors: An analysis of patients treated on the SIOP-WT-2001 protocol in the UK-CCLG and GPOH studies (2001–2020)
    Cancer 129:1930-1938, 2023; doi:10.1002/cncr.34734; ->Abstract

14. **Michael V. Ortiz, Christa Koenig, Amy E. Armstrong, Jesper Brok, Beatriz de Camargo, Annelies M.C. Mavinkurve-Groothuis, Thelma B. Velasquez Herrera, Rajkumar Venkatramani, Andrew D. Woods, Jeffrey S. Dome, Filippo Spreafico**
    Advances in the clinical management of high-risk Wilms tumors
    Pediatr Blood Cancer 70:e30153, 2023; DOI:10.1002/pbc.30153; ->Abstract

15. **Sabine Irtan, Aurore Coulomb-Lhermine, Camille Lanz, Marie-Dominique Tabone, Claudia Pasqualini, Benoit Dumont, Estelle Thebaud, Isabelle Guellec, Arnauld Verschuur**
    Number of lymph nodes sampled in SFCE/SIOP 2001 patients with Wilms tumour: Is the goal of more than six achievable?
    Pediatr Blood Cancer 70:e30107, 2023; DOI:10.1002/pbc.30107; ->Abstract

16. **Clemens-Magnus Meier, Rhoikos Furtwängler, Marvin Mergen, Nils Welter, Patrick Melchior, Jens-Peter Schenk, Christian Vokuhl, Leo Kager, Sabine Kroiss-Benninger, Stefan Wagenpfeil, Norbert Graf**
    Impact of Time to Surgery on Outcome in Wilms Tumor Treated with Preoperative Chemotherapy
    Cancers 15:1494, 2023, 15, 1494. https://doi.org/10.3390/cancers15051494; ->Abstract

17. **Walz AL, Maschietto M, Crompton B, Evageliou N, Dix D, Tytgat G, Gessler M, Gisselsson D, Daw NC, Wegert J**
    Tumor biology, biomarkers, and liquid biopsy in pediatric renal tumors.
    Pediatr Blood Cancer. 2023 Jan 2:e30130. doi: 10.1002/pbc.30130. Epub ahead of print; ->Abstract

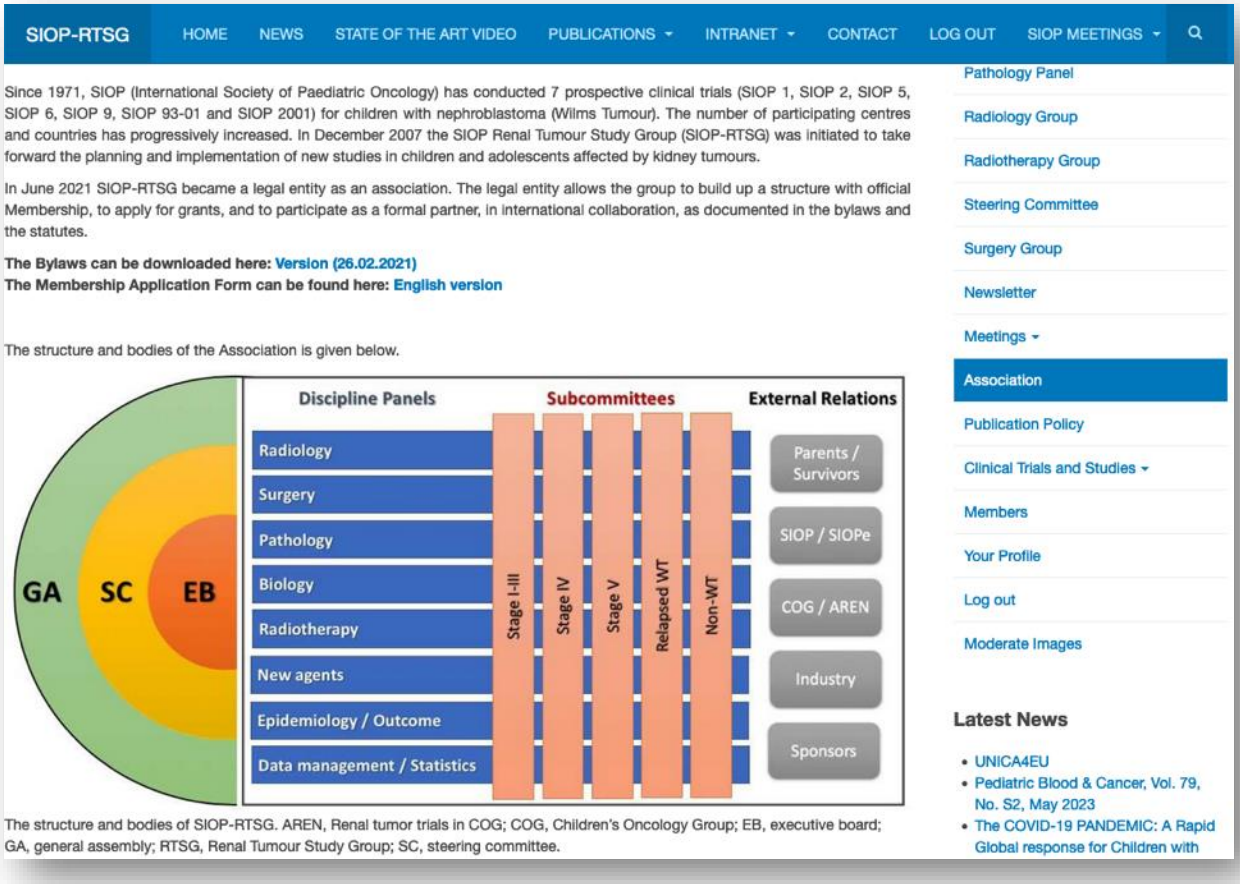
18. **Fialkowski E, Sudour-Bonnange H, Vujanic GM, Shamberger RC, Chowdhury T, Aldrink JH, Davick J, Sandberg J, Furtwaengler R, Mullen E**
The varied spectrum of nephroblastomatosis, nephrogenic rests, and Wilms tumors: Review of current definitions and challenges of the field.
Pediatr Blood Cancer 22:e30162, 2022; doi: 10.1002/pbc.30162; ->Abstract

19. **Artunduaga M, Eklund M, van der Beek JN, Hammer M, Littooij AS, Sandberg JK, Schenk JP, Servaes S, Singh S, Smith EA, Srinavasan A, Khanna G**
Imaging of pediatric renal tumors: A COG Diagnostic Imaging Committee/SPR Oncology Committee White Paper focused on Wilms tumor and nephrogenic rests.
Pediatr Blood Cancer 29:e30004, 2022. doi: 10.1002/pbc.30004; ->Abstract

20. **McAleer MF, Melchior P, Parkes J, Pater L, Rübe C, Saunders D, Paulino AC, Janssens GO, Kalapurakal J**
Harmonica consensus, controversies, and future directions in radiotherapy for pediatric Wilms tumors.
Pediatr Blood Cancer e30090, 2022; doi: 10.1002/pbc.30090; ->Abstract

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. ➔ **https://siop-rtsg.org**



Upcoming Meetings

12th to 15th of March, 2024	Chicago, IL United States	COG Spring Meeting (invitation only)
5th to 10th of April 2024	San Diego, CA United States	AACR Annual Meeting 2024
13rd to 17th of May 2024	Milan, Italy	5th Annual SIOP Europe Meeting
31st of May to 4th of June 2024	Chicago, IL United States	ASCO Annual Meeting 2024
6th to 7th of June 2024	New York, NY United States	12th Int Paediatric Renal Tumour Biology Conference
16th to 18th of September 2024	Porto, Portugal	SIOP-RTSG Committee Meeting
24th to 27th of September 2024	New Orleans, LA United States	COG Fall Group Meeting (invitation only)
13th to 174th of September 2024	Barcelona, Spain	ESMO
17th to 20th October 2024	Honolulu, HI United States	56th Congress of SIOP

Impressum

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