Newsletter

SIOP Renal Tumour Study Group

Issue 6 2020

Content

Editorial

Last year we anticipated a busy year for the SIOP-RTSG, but this year turns out to be very different and much more challenging for all of us because of the COVID-19 pandemic. Regular face to face meetings were no longer possible after the successful SIOP-RTSG meeting in Rio de Janeiro in March organized by our Brazilian friends. Even then not all members of our group were able to travel resulting in a hybrid (live plus teleconference) meeting. Then the 10th International Biology Meeting planned for Marseille in September was also only possible as a virtual meeting, as it was the case also for the SIOPe and SIOP congress this year. Nevertheless, the scientific content was excellent in all of these meetings and we are now experts in attending and running virtual conferences, but we hope that they are not going to become 'new normal' since we are all missing meeting friends and the social dimensions of our meetings. Despite these circumstances the UMBRELLA Study is continuously recruiting patients as expected during the whole year. More than 500 patients are already enrolled in the UMBRELLA Study from 14 different countries representing many participating hospitals, and more countries will be joining us very soon. Thanks to all of you who are making the UMBRELLA Study a real success story. Randomet, a prospective randomized phase III trial for metastatic nephroblastoma, will start to recruit patients at the beginning of the next year as all the necessary regulatory issues with their bureaucracy are solved. Two other activities need to be mentioned here as well. First, we hope that the SIOP-RTSG Association can be founded within the next 6 months that brings a lot of advantages to our group. Secondly, we are happy that the Young Investigators (YI) group will join the SIOP-RTSG very soon. During our last Steering Committee Meeting YIs from SIOPe and from COG were invited to discuss how to proceed. Please see here a photo of this online event:

We hope you find interesting information in this newsletter, but most of all we wish you a Merry Christmas and a healthy New Year, for you, your families and friends.

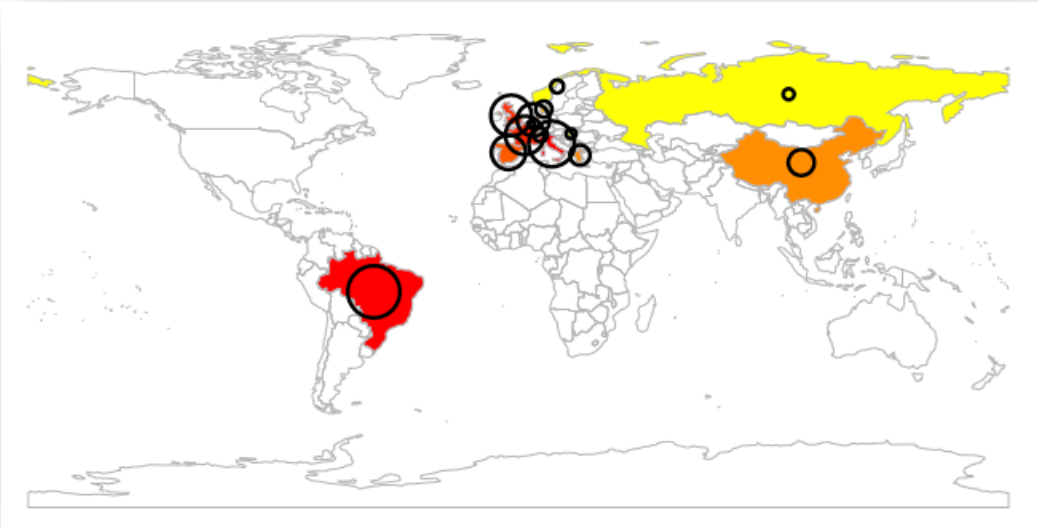
Norbert Graf

Gordan Vujanic

UMBRELLA

By Norbert Graf and Marry van den Heuvel-Eibrink

The UMBRELLA Study is now running since June 2019 and we have already registered 519 patients. This includes 443 patients with the primary diagnosis of a nephroblastoma and 52 with a non-Wilms tumour. 24 patients were registered having a relapse. Most of these relapses are from patients being treated in SIOP 2001. The worldwide accrual rate is shown in the figure below (created by Harm van Tinteren). On a regular monthly basis updates of the trial are sent to you via the newsflash that can also be found in the intranet of our website. At the moment it is too early to report about results of the study. All countries, who also want to participate, can be initiated as soon as they have signed the contract with the sponsor and ethical approval is available. There is always the need for a National Principal Investigator (PI). The training of the ALEA remote data entry system (RDE) needs to be finished by everybody who will use the system. The PI has to provide a list of participating members of their National team for Oncology, Radiology, Surgery, Biology, Pathology and Radiotherapy so that access to ALEA can be given. The National center is then responsible for initiating their local centers, so that all patients of their National nephroblastoma group can be enrolled in the UMBRELLA Study.



Reference centers in the different participating countries have started to work. In case of difficulties the chairman and chairwomen of the different panels of SIOP-RTSG are always helpful to guarantee an optimal treatment for all patients with a renal tumor in children, adolescents and young adults.

For all participating countries regular meetings with the National coordinators will be held, so that an intensive contact with them is guaranteed. In case of burning questions, the chairman and vice chairwomen and the SIOP Office Team can always be reached by email.

The main goal of the UMBRELLA study is to find new biomarkers for a better stratification of treatment in upcoming trials. To be successful, it is very important that parents or legal guardiennes give their informed consent for participating in the research projects of UMBRELLA. For the centers material transfer agreement (MTA) for biomaterial are provided and can be downloaded from our intranet.

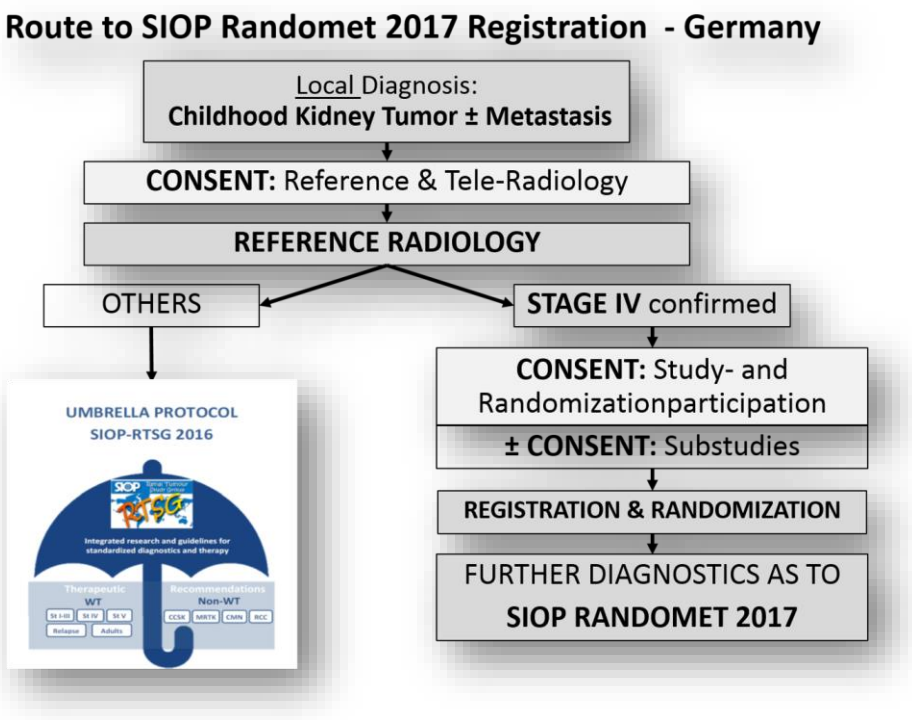
Hopefully in 2021 we can present first statistical results in our SIOP-RTSG committee meeting that will hopefully be able to take place as a face to face meeting in Utrecht / The Netherlands from the 24th to 25th of June 2021.

News from SIOP Randomet 2017 – A randomized trial for stage IV childhood nephroblastoma

By Arnauld Verschuur and Rhoikos Furtwängler

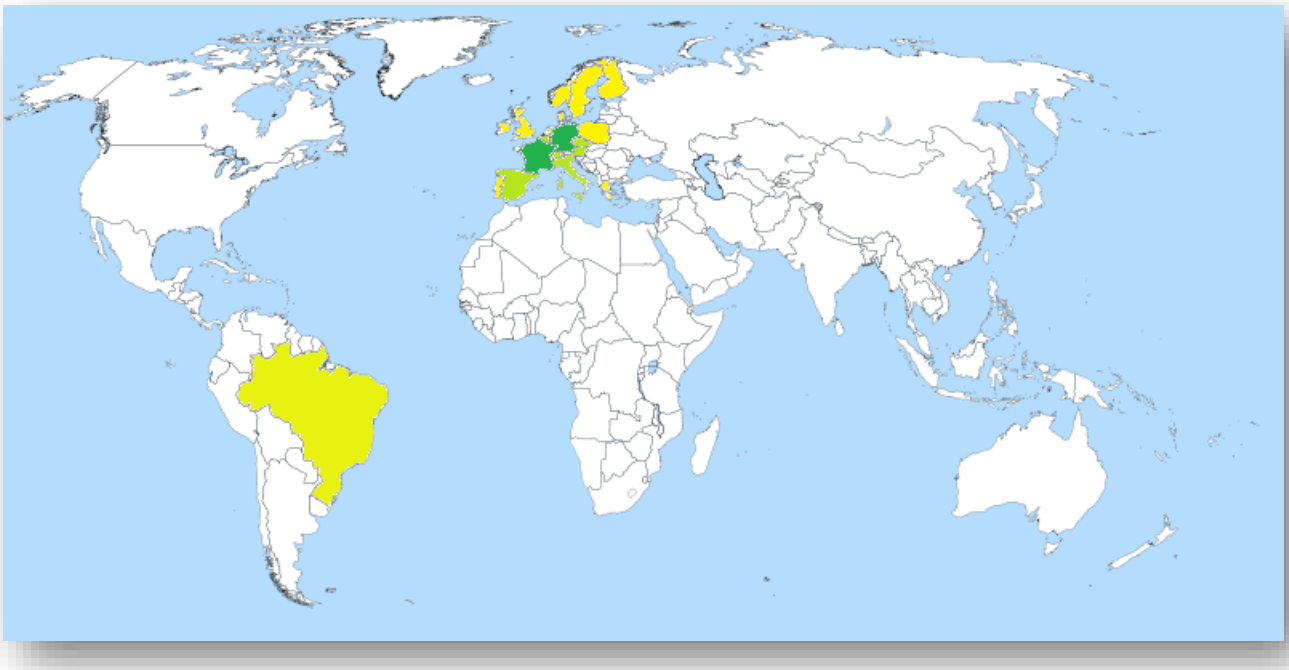
It has been a long and enduring work of the STAGE IV subcommittee from an initial idea created in 2013 to the approved protocol for the "*Randomized multi-centre open-label non-inferiority phase 3 clinical trial for patients with a stage IV childhood renal tumour comparing upfront Vincristine, Actinomycin-D and Doxorubicin (VAD, standard arm) with upfront Vincristine, Carboplatin and Etoposide (VCE, experimental arm)".* After a tiresome work submitting the protocol and required documents to more than 40 ethic committees in Germany and France – not only in theory a heavy (work) load (Compare Photo), the randomized prospective trial SIOP-Randomet 2017 has been given authorization by national competent authorities and ethic committees in France (10/2020) and Germany (12/2019). The Sponsor GPOH and its CRO "Pädiatrisches Forschungsnetzwerk" together with the trial office in Homburg/Saar are putting a maximum effort in facilitating further submissions and opening of the study in other countries. The majority of the 47 centres throughout Germany are about to open within the next months and will soon be followed by 29 centres in France. Submissions are ready to be submitted in Switzerland and under preparation in the Netherlands, Belgium, Czech Republic, Austria, Italy, Spain and Brazil and we hope that further countries as for example Denmark, Norway, Sweden, Portugal, Greece, Poland and UK will soon follow.

Dr. Yvonne Braun (Lead Project Manager, Study Center Homburg) packing and posting the initial submission in summer 2019 kindly helped by ObTiMA Informatician Benedikt Roncossek in front of the Volkswagen needed for such "Heavy Load".



Flow Chart depicting the route to SIOP Randomet 2017 inclusion in Germany.

For inclusion of patients in the trial, a central requirement will be a real-time initial and response reference radiology to be organized on a national level (Compare Figure 2 - Flow Chart Germany). Once the reference radiology diagnosis of a stage IV childhood kidney tumour is established, randomization will be feasible remotely on ALEA or over the national coordinating centre. Despite Corona Pandemic delaying many procedures we hope to be able to randomize the first patients in early Spring 2021 in France, Switzerland and Germany and to recruit annually roughly 80-100 patients to answer our question until 2026/27 by accruing 406 patients in total.



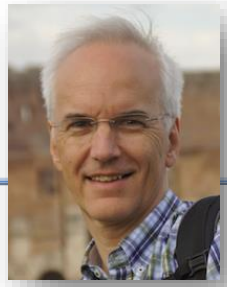
Coloured map of the world giving an impression in which countries submission is planned (yellow), being prepared (light green) or already accepted (dark green).

Data Management

By Harm van Tinteren and Prakriti Roy

In March 2018, the SIOP-RTSG office, data management and trial management activities were moved to the Princess Máxima Center location in Utrecht, the Netherlands. Since March 2019, the SIOP-RTSG office team, together with Prof Dr. Norbert Graf, initiated 13 countries and 4 large regions and supported registration of the first 484 kidney tumor patients in SIOP-RTSG-2016-UMBRELLA. Since the first of September 2020, the data-analysis and statistical activities and historical data from SIOP 2001 and 93-01, also moved to Utrecht together with Dr. Harm van Tinteren. The SIOP-RTSG office team is now actively supporting the launch of the Randomet study, together with the GPOH team, and Prof. Dr. Rhoikos Furtwangler and Dr. Arnauld Verschuur.

***SIOP-RTSG office team**. Dr. Harm van Tinteren, statistician SIOP-RTSG, Drs. Prakriti Roy, data scientist and cDM (laptop), Prof. Dr. Marry M van den Heuvel-Eibrink, vice-chair SIOP-RTSG and coordinator SIOP-RTSG team, Drs Chantal van Kempen-van Overbeek and Drs. Sandra van der Kroef-de Haas, cTrial managers.*



News from Biology

By Manfred Gessler

The abbreviated online Pediatric Renal Tumor Biology Meeting only allowed to showcase a fraction of recent progress in biological studies (see meeting report). Emerging and smaller studies on many topics could not be presented, so stay tuned for next year's meeting in Marseille for the full update.

The greatest potential for translational progress is certainly ascribed to liquid biopsies that may provide molecular biologists and clinicians with a new view and much more data points to evaluate. This should encourage everyone to take on the tedious task of collecting plasma samples already before chemotherapy and at multiple time points thereafter as indicated in the protocol. Only with sufficient numbers of longitudinal samples at hand can we evaluate the true power of this technology. In many countries adherence to these collection regiments can still be improved.

Current registration numbers suggest that biobanking coverage in general may still be increased: out of 457 enrolled patients as of October 2020, around 75% consented to biobanking. While participation certainly is a personal and voluntary decision, proactive endorsement by all treating physicians may help to further increase this number to achieve complete coverage throughout the study. Especially the less frequent cases of relapse, bilateral, familial or adult Wilms tumor as well as all non-Wilms tumors should receive high priority to establish a comprehensive collection.

There are large-scale next generation sequencing efforts currently under way with samples from UK/Germany and global pediatric cancer sequencing programs in UK/France as well as parallel efforts in the US. Together these will hopefully soon lead to the establishment of dedicated Wilms tumor NGS panels. They will allow us to screen large numbers of cases of tumors or liquid biopsies and explore transfer of such tests into clinical scenarios.
Recent data from methylation profiling led to renewed interest in epigenetic alterations in Wilms tumors (Coorens et al., 2019; Brzezinski et al., 2020). The work of Coorens et al. strongly suggest that aberrant H19 methylation at chromosome 11p15 may lead to clonal hyperproliferation in normal tissue as a precursor to Wilms tumor formation. In the second paper, the epigenetic status at 11p15 is shown to yield an interesting classification of tumors with differential propensity for bilateral occurrence or relapse and other parameters. Extension of these finding in larger cohorts will be needed to corroborate these findings.

References:

- Brzezinski, J., Choufani, S., Romao, R., et al. (2020). Clinically and biologically relevant subgroups of Wilms tumour defined by genomic and epigenomic analyses. *Br J Cancer*. doi:10.1038/s41416-020-01102-1
- Coorens, T. H. H., Treger, T. D., Al-Saadi, R., et al. (2019). Embryonal precursors of Wilms tumor. *Science, 366*(6470), 1247-1251. doi:10.1126/science.aax1323

Pathology

By Gordan Vujanic

As for everyone else, the period behind us (and probably ahead, for a while, at least) was difficult and challenging for our work. With the UMBRELLA Study picking up, all Pathology Panels have started receiving more cases, and they are successfully dealing with them. There is still uncertainty when some countries will officially start recruiting cases and their Pathology Panel doing rapid central pathology review (Poland, Japan, for example), and we hope it will happen soon. There is also uncertainty how central pathology review will be done in China, and that is something that will need to be discussed and addressed with our Chinese collaborators.

In the meantime, we managed to have 2 review meetings in 2020, just before the pandemic. The first meeting was in Paris (6-7 February 2020), where we reviewed ~200 cases which were nicely prepared by our host Aurora Coulomb. The meeting had more participants that usual, with guests from the Netherlands, UK, Hungary and France, who joined us in order to gain experience and insight in how we work.

The second review meeting was in Rio de Janeiro (11-12 March) just prior to the SIOP-RTSG Annual meeting. Our host was Isabela Werneck and we reviewed ~130 Brazilian cases. We also found time to explore a beautiful city of Rio. But worries over the corona pandemic made us all concerned about what we were facing next.

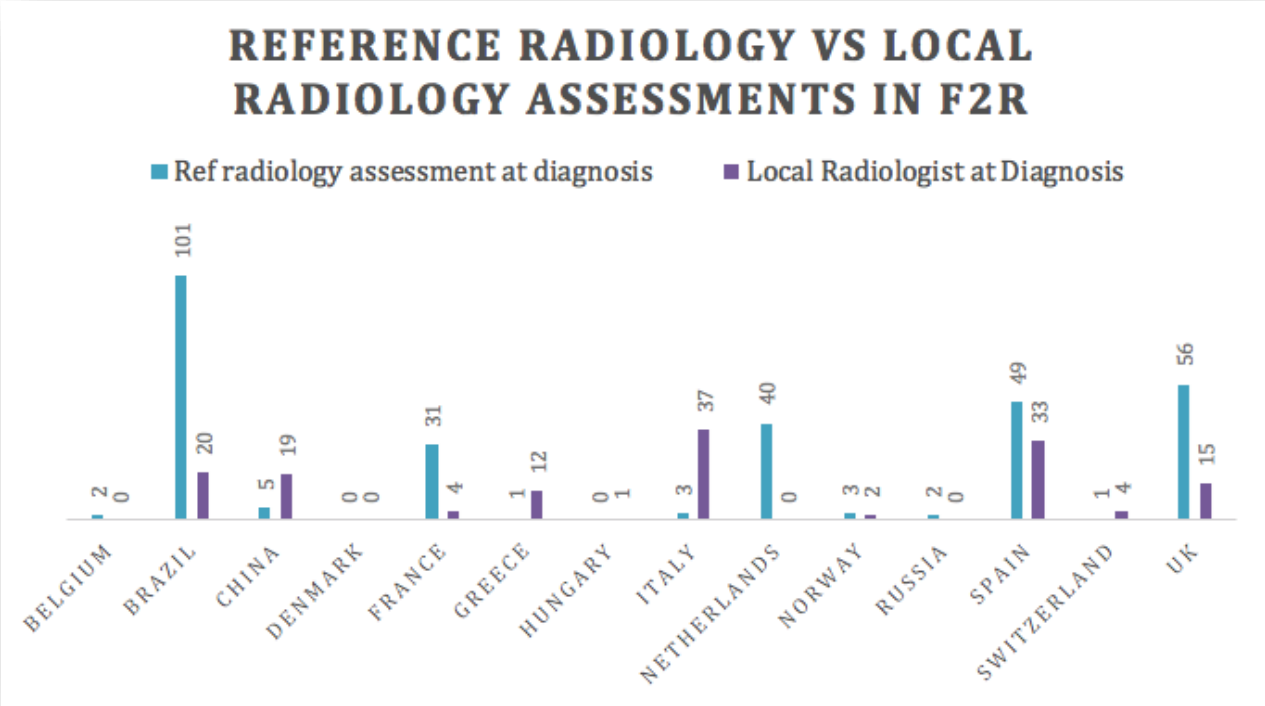
Although we had plans for more review meetings in 2020, none of them took place, and once the pandemic is over, we will be very busy since cases have been reviewed by the Panels, and we'll have to have a series of frequent meetings in order to catch up with accumulated cases. Ronald is preparing a virtual review meeting and we will see how successful it is going to be, and whether we will be able to do it for at least centres where digital pathology is available.

Our members have published some papers on pathology topics (please see the list of publications) and actively participated in other projects.

News from the Radiology Panel

By Jens-Peter Schenk and Hervé Brissé

The UMBRELLA Study is characterized by a very high quality of diagnostic reports by central radiology review. Since opening of the Study radiologists of involved countries try to achieve a high number of local and reference reports. Up to November 147 local F2R forms and 294 reference F2R forms (Date of analysis) were registered in ALEA. Despite of the Covid pandemia in 2020 registration of patients with radiology forms works, organisation of reference radiology in different countries is an ongoing process which needs to be developed by the native study centers and the radiology panel members.



(ALEA report, 9.11.2020)

In June 2020, the SIOP-RTSG radiology panel (project managers J. van der Beek and A. Littooij) initiated a study focusing on the MRI-characteristics of pediatric renal tumors. This study aims to combine the expert knowledge within the group. Following the ‚Delphi method', this study has the purpose to identify imaging characteristics that should be taken into consideration when assessing MR-images for the diagnosis of pediatric renal tumors. A Delphi study is a group facilitation technique and an iterative multi-stage process, designed to create consensus statements or guidelines from expert opinions, through a series of structured questionnaires. As part of the process, the responses from each round are fed back in summarized form to the participants, who are given an opportunity to respond again to the emerging data. For this Delphi Study, a two round online questionnaire process was employed. The selection of potential experts in the field of pediatric oncologic radiology were radiologists identified in the SIOP-RTSG radiology panel. These potentially participants received an invitation letter, including a request to introduce other pediatric radiologists as potential participants through a ‚snowballing' technique. In order to participate in the study, the invited radiologists had to meet at least one of the following inclusion criteria:

>= 5 years of experience in MR-imaging of pediatric renal tumors and/o

>= 50 MRI-scans of pediatric renal tumors in the past 5 years

In June 2020, 39 radiologists were invited to participate in the study, of which 23 (representing 14 countries) completed the first online questionnaire and 19 participants completed the second questionnaire. We are currently in the process of analyzing the data.

Project manager Justine van der Beek presented the Delphi project on the SIOP-RTSG meeting in March 2020 in Rio de Janeiro to the present and online present participants.
Further research projects in renal tumors in childhood with the impact of SIOP-RTSG radiology panel members cover the diagnostic potential of dwi (diffusion weighted imaging) imaging for risk stratification and differential diagnosis of renal tumors and the role of biopsy in initial diagnosis.

Future projects should address the evaluation of recently published MRI studies to renal tumors in childhood in view of the results of the Delphi project.

Next meeting of the group is planned at the SIOP/RTSG meeting in Utrecht/the Netherlands 2021.

Current SIOP-RTSG core group members of the radiology panel are:

Jens-Peter Schenk, Germany, chair	Ana Coma, Spain
Hervé Brissé, France, co-chair	Maria Gavra, Greece
Annemieke Littooij, the Netherlands	Dorota Sosnowska, Poland
Enrique Ledermann, Brazil	Luc Breysem, Belgium
Carlo Morosi, Italy	Gabor Rudas, Hungary
Ostein Olsen, UK	Enno Stranzinger, Switzerland
Karoly Lakatos, Austria	

Selection of recommended literature to initial imaging and current research of the panel:

- The role of imaging in the initial investigation of paediatric renal tumours. Watson T, Oostveen M, Rogers H, Pritchard-Jones K, Olsen Ø.Watson T. Lancet Child Adolesc Health. 2020 Mar;4(3):232-241.
- Diffusion-weighted MRI in the assessment of nephroblastoma: results of a multi-center trial. Hötker AM, Lollert A, Mazaheri Y, Müller S, Schenk JP, Mildenberger PC, Akin O, Graf N, Staatz. Abdom Radiol (NY). 2020 Oct;45(10):3202-3212.
- From Wilms to kidney tumors: which ones require a biopsy? Brisse HJ, de la Monneraye Y, Cardoen L, Schleiermacher G. Pediatr Radiol. 2020 Jul;50(8):1049-1051.. Epub 2020 Apr 5.
- Indications and results of diagnostic biopsy in pediatric renal tumors: A retrospective analysis of 317 patients with critical review of SIOP guidelines. de la Monneraye Y, Michon J, Pacquement H, Aerts I, Orbach D, Doz F, Bourdeaut F, Sarnacki S, Philippe-Chomette P, Audry G, Coulomb A, Fréneaux P, Klijanienko J, Berrebi D, Zucker JM, Schleiermacher G, Brisse HJ. Pediatr Blood Cancer. 2019 Jun;66(6):e27641.
- Whole-tumor apparent diffusion coefficient measurements in nephroblastoma: Can it identify blastemal predominance? Littooij AS, Sebire NJ, Olsen ØE.. J Magn Reson Imaging. 2017 May;45(5):1316-1324.

News from the Radiotherapy Panel
Update of integration of Modern Irradiation Concepts and Technique

By Christian Rübe and Patrick Melchior

Review

The SIOP-Renal Tumour Study Group consensus statement on flank target volume delineation for highly conformal radiotherapy

Geert O Janssens*, Patrick Melchior*, Joeri Mul, Daniel Saunders, Stephanie Bolle, Alison L Cameron, Line Claude, Kristin Gurtner, Kees P van de Ven, Martine van Grotel, Semi Harrabi, Yasmin Lassen-Ramshad, Naomi Lavan, Henriette Magelssen, Xavier Muracciole, Tom Boterberg, Henry Mandeville, Jan Godzinski, Norbert Graf, Marry M van den Heuvel-Eibrink, Christian Rübe

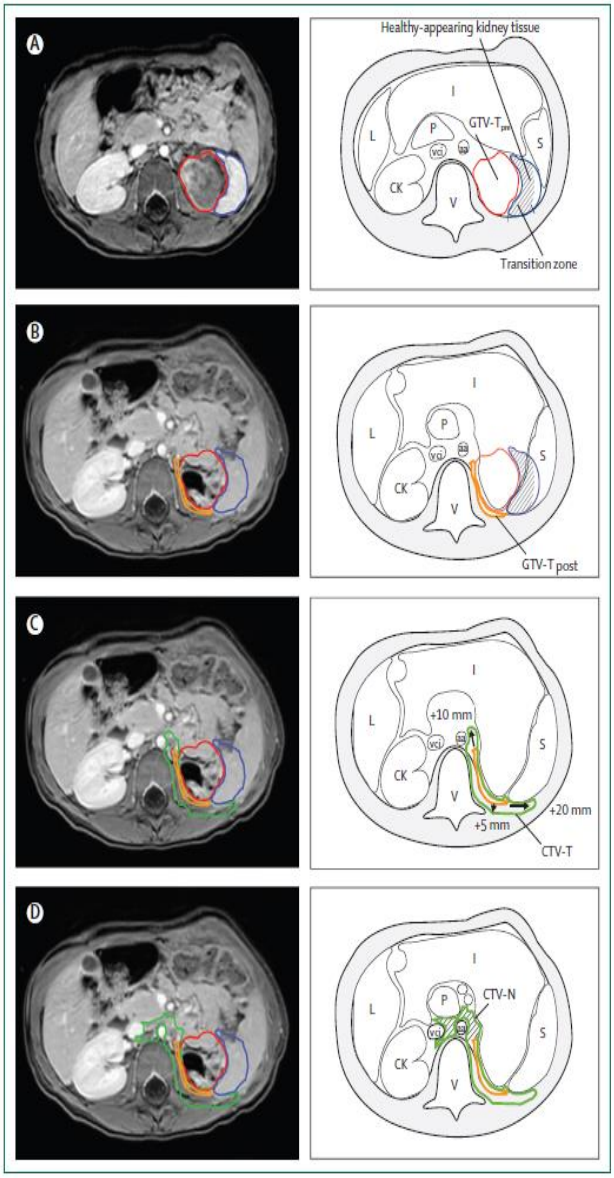


Figure 2: Stepwise approach to highly conformal GTV and CTV delineation

In the November 2020 edition of *The Lancet Childhood and Adolescent Health*, radiation oncologists of the SIOP-RTSG present their new approach on **flank target volume delineation**, taking into account the shift of organs after nephrectomy.

These highly-conformal target volumes in combination with advanced image-guided radiotherapy techniques can result in a significant reduction of the total amount of normal tissues receiving a higher radiotherapy dose and so radiotherapy-induced late toxicity.

Although deemed to be amended to the new version of the UMBRELLA-RTSG-2016 protocol, radiation oncologists **strongly recommend participation in a planned prospective trial with central review** of the target volumes in order to map unforeseen events by using the new compared to the conventional target volumes.

DOI: 10.1016/S2352-4642(20)30183-8

News from the Surgical Panel

By Jan Godzinski

Merry Christmas and Happy New Year!
STAY SAFE (please)

Dearest Friends,
I'd like to send You just a few words on how the surgical live runs in this difficult pandemic time in a paediatric surgical oncology centre. Despite the lock-down in many of our countries surgeons keep working. Conditions however became different.
In this short letter I would like to share with You the way we tried to manage those issues at my place. I will be more than happy if You considered our experience useful for You. Also please do not hesitate to comment. I am more than expecting advices and suggestions.

A Child with an Oncology Problem In a Paediatric Surgery Department
The Wroclaw/Marciniak Hospital Example

Objectives
All life-threatening diseases are to be treated at a proper time. No delay is accepted.
Transmission of COVID is a crowd-dependent and an unprotected contact-dependent.

- ➔ No crowd in the wards is accepted.
- ➔ The number of patients staying in a department should allow for their isolation in a separate room each. Parents (1 person) are allowed, but they should not circulate between rooms, home and the hospital and stay with her/his kid.

Who is treated?

1. Emergency and **oncology** cases have highest priority.
2. Patients touched with serious and chronic diseases and those who require staged surgical (already scheduled/planned) treatments have intermediate priority.
3. Regular cases have low priority: they are invited and treated when places in the department and OP Block are free.

Organisation of Department

1. **Buffer Unit:** separated from the rest of Department, sluice-protected part for children of unknown, suspicious or positive COVID situation. Each child stays in a separate autonomous and sluice-protected room with his (1) parent. Stuff is exclusive and protected like for COVID.
2. **Regular Unit:** the unit for children who were recently (4 days before expected surgery the latest) tested for COVID and are negative. One patient +/- one parent in one room are hosted at max (!). Stuff is not involved in any other work; stays only in the Regular Unit. Moderate self-protection and social distance measures are mandatory for patients, parents and stuff.
3. **ICU:** 4 places in 2 separate rooms for post-op patients and 1 isolated place for an emerging surgical patient with unknown or positive COVID status. The stuff for the isolated room is exclusive; ICU is sluice-protected as well as its isolation station (next one).
4. **Operating theatres**
   One so called "COVID OP-theatre" is blocked for COVID suspected- or positive surgical cases only, it is separated from the rest of the block.

How to enter Department

1. Oncology (and other serious) cases: +/- a parent intending to stay are tested prior to admission (PCR). They are admitted to the Regular Unit if negative. If they are positive – surgery is postponed when possible, but if it is not possible – such a patient is invited to the isolated room in the Buffer Unit and are operated on with all the precautions in the "COVID OP-theatre" by an adequately protected stuff. Postoperative stay runs in the Buffer Unit respecting the standards of the antiviral precautions. If only possible from the surgical reasons, those patients are transferred to Department of Paediatric Infectious Diseases for the late post-op treatment. Surgeons visit those children if needed. If this is an oncology patient, also an oncologist follows them and even chemotherapy can be administered there.
2. New urgent cases are all tested "at entrance" with an antigen fast test, but until the PCR results comes, they stay in the Buffer Ward. If they need an immediate surgical care, it is provided in conditions related to the testing results. If the fast antigen test is negative, precautions are less but still higher than in case of PCR negative results. Regular OP Theatre is open for them, but the stuff is prevented. In case of a positive antigen test and a need for immediate surgery, the case is taken like COVID +.

Please comment! No dead-line… With the above measures we experienced only a few department-related infections both among the patients and the stuff. More had a private-social origin (…).

Merry Christmas And A Prosperous New Year For All of You, Your Families, Teams and Friends!!!

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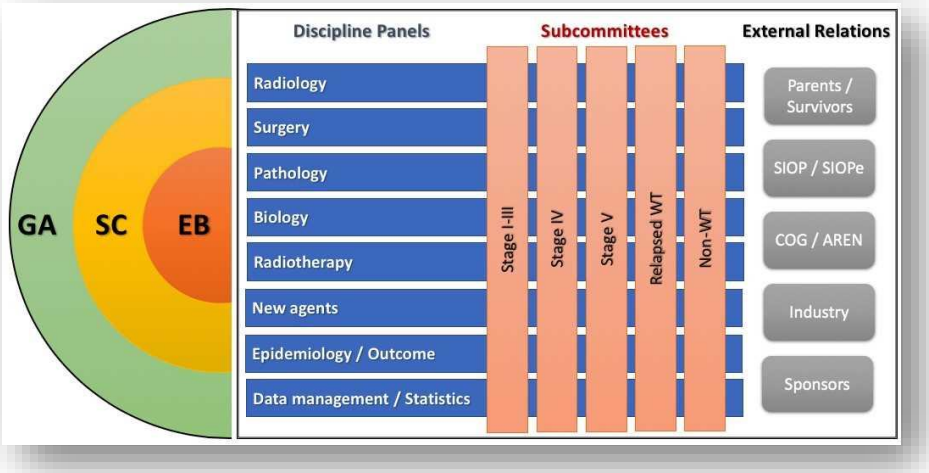
Information about the Association

By Marry van den Heuvel-Eibrink and Norbert Graf

The SIOP-RTSG group started their activities 40 years ago. Currently, the group is preparing the official establishment of the SIOP-RTSG Association, in order to become a legal entity, which will enable to adhere to current regulations and to participate in international networks as an official partner. It is expected that the Foundation process will be finalized in the first quarter of 2021 by the Steering committee of the SIOP-RTSG. Most importantly the Association will undertake actions to guarantee that children and adolescents with a renal tumour will receive the best diagnosis and treatment based on up to date knowledge. In addition, some specific goals and objectives will be:

- develop evidence- and expert-based guidelines for diagnosis, care and long-term surveillance of children and adolescents with renal cancer for dissemination around the world
- promote the education and training of health professionals in the field of renal tumours
- provide expert opinion to physicians who treat patients with renal tumours and assist them with multidisciplinary clinical decisions in requested cases
- improve care by promoting and supporting clinical trials and studies in European and non-European countries for children and adolescents with renal tumours
- promote and support collaborative research in basic and translational research and new drug development for children and adolescents with renal tumours with all possible stakeholders, including industry
- improve information to patients, their families, and stakeholders both in relation to health care and to scientific research
- endorse collaboration with families and long-term survivors of renal tumors

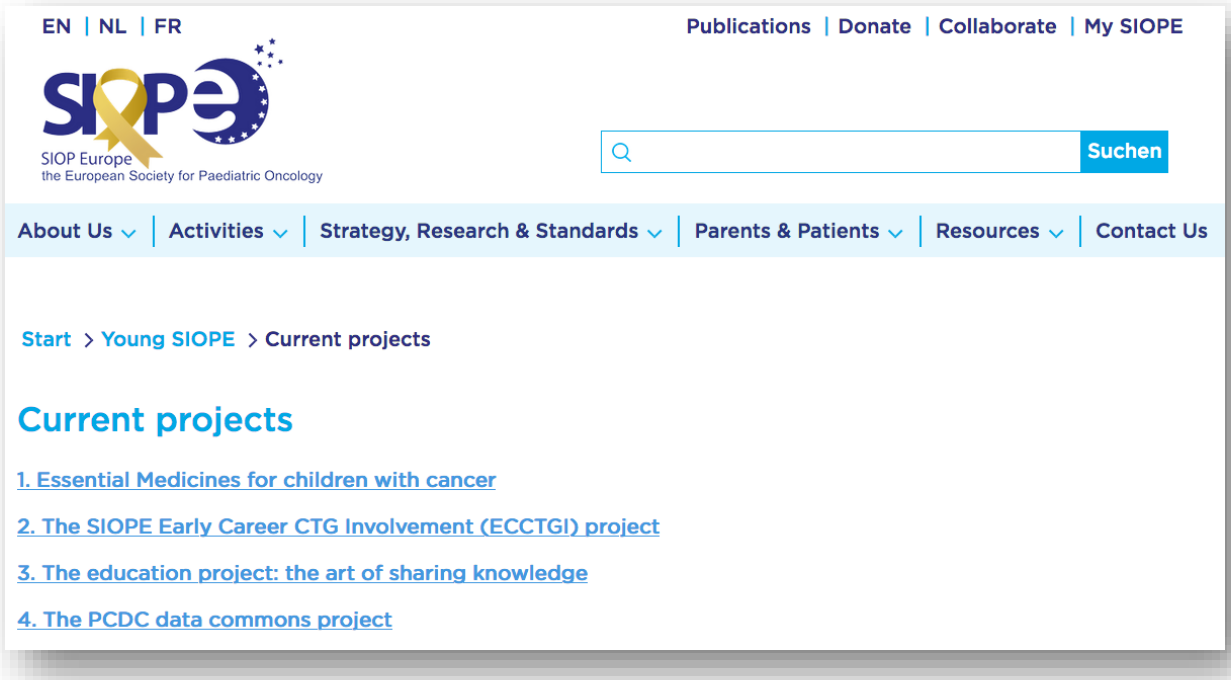
The Association will be managed by an Executive Board (EB), that will be advised by a Steering Committee (SC) The structure and bodies of the association is shown in the following figure. The General Assembly (GA) is the highest and final decision-making body of the Association. The GA is defined as the assembly of SIOP-RTSG members and is the final decision-making body of the Association. More details will be explained and discussed at our next SIOP-RTSG committee meeting in 2021.



RTSG-SIOP and Young Investigator group in SIOP-Europe initiate collaboration

By Jesper Brok and Filippo Spreafico

There is a mutual interest among the SIOPe Young Investigator (YI) and SIOP-RTSG to collaborate. SIOPe YI (part of the SIOP YI-network) represents the interests of young investigators mainly in Europe within the field of paediatric oncology. The aims are to provide a platform for young investigators to develop research and scientific skills and to facilitate an international research network with other young investigators in paediatric oncology. With the increasing workload and upcoming research projects adjacent to the UMBRELLA protocol such aims provide the opportunity to collaborate, educate and incorporate SIOPe-YI members in the RTSG subcommittees and panels. Likewise, a bridge between experienced investigators and younger colleagues has recently been established through the renal tumour essential medicine projects – a European/WHO project that aims to map the key medicines (and ensure availability) that are needed for each type of child cancer. Accordingly, members of the SIOPe-YI and the essential projects were invited to participate (Christa Koenig, Nicolas Herold, Reineke Schoot and Emma Seaford) and to introduce each other for exchanging ideas at the RTSG steering committee meeting in November 2020. Furthermore, Michael Ortiz leading the Young oncologist's group of the COG, who has experience with similar mentorship, grant applications and research in COG shared his experience at this meeting as well. In conclusion, a fruitful discussion was initiated, and it was agreed that the SIOPe-YI will identify a younger colleague who should be the link between the two groups. Following this decision, more specific tasks and expanding the subcommittees with younger colleagues are agreed upon.



https://siope.eu/young-siope/ and https://siope.eu/current-projects-young-siope

Some participating countries

Moscow, Russia

Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation
By Denis Kachanov

Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology is the leading specialized comprehensive center dedicated to children with benign hematological disorders and all types of childhood cancer, including renal tumors. The center has received the special designation from the Ministry of Healthcare as a national center and serves as a reference center for tumor pathology, radiology, molecular biology. The center is responsible for the organization of the multicenter cooperation in the field of pediatric hematology oncology in Russia. A multidisciplinary team dedicated to pediatric renal tumors has been established and consists of pediatric oncologists, pediatric surgeons, radiologists, radiation oncologists, pathologist and molecular oncologists. The center provides all types of medical care from the initial diagnosis to chemotherapy, complex surgical procedures (NSS) and radiation therapy. Each patient with renal tumors is discussed during weekly multidisciplinary solid tumors board. The center has extensive experience in treating pediatric patients with renal tumor, including bilateral Wilms tumor, according to SIOP2001 protocol but up to now outside the clinical trial. SIOP-RTGS Umbrella protocol was opened in May 2020 and 4 patients have been included so far.

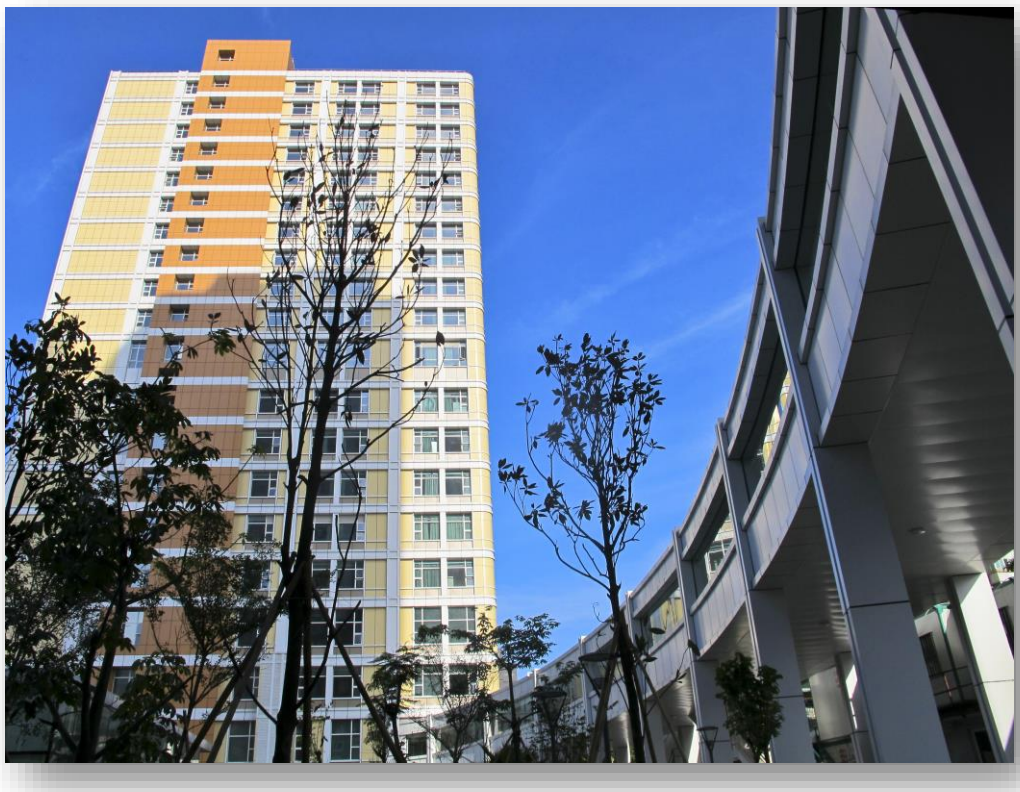
Guangzhou, China

By Xiaofei Sun and Zijun Zhen

The Sun Yat-sen University Cancer Center (SYSUCC) is one of the four earliest cancer hospitals established in China and located in the city of Guangzhou. It is the largest cancer center in South China, which integrates medical treatment, teaching, scientific research and cancer prevention. Its disciplinary position and comprehensive strength are at the leading level in China. SYSUCC was also one of the earliest cancer centers in China which established a department of pediatric oncology.

Nowadays, around 450 new patients with pediatric oncology were diagnosed and treated in SYSUCC each year, and among them about 40 pediatric patients were diagnosed as renal tumor. This is the first time we participate in the SIOP-RTSG study. We have translated the UMBRELLA protocol into a Chinese version for the purpose we practice more easily in China. Our multidisciplinary team can meet the requirements of UMBRELLA research, but we cannot send the biological samples of our patients abroad for further studying based on the Chinese laws and rules.

In some degree, the UMBRELLA research is complex for Chinese physicians, but we are trying our best to overcome all the difficulties. We joined the UMBRELLA study on May 20, 2020. At present, 11 pediatric patients with renal tumor have been enrolled in the UMBRELLA study from May 20, 2020 to November 20, 2020, and everything is going well in our cancer center. We will complete our own multicenter clinical trial of pediatric Wilms tumor by the end of this year. After that all patients with pediatric renal tumor in our cancer center will be enrolled in UMBRELLA study.



We plan to expand more hospitals to participate the UMBRELLA study next step. But this plan needs to be approved by Chinese government. We are currently going through the relevant procedures.

Shanghai, China

By Kuiran Dong

Children's Hospital of Fudan University ranks top 2 in China, among which the department of pediatric surgery enjoys a nationwide reputation. There are about 25 new-onset renal tumor annually. We have obtained local institutional IRB approval to join the SIOP-RTSG UMBRELLA study. Since mid-2018, we have been using UMBRELLA as the reference protocol for renal tumors we are treating in our center. The department of radiology is providing latest multi-modality imaging which can differentiate renal tumors from other retroperitoneal malignant solid tumors. Meanwhile, pathologists are extensively experienced in tumor pathology and biology. We have completed tumor banking, as well as patient-derived cultivation and xenotransplantation.

Our team will collect detailed clinical information of each patient willing to participate in the SIOP RTSG UMBRELLA study, and full informed consent will be obtained from each patient.

We are the first children's hospital in China to join this program, and greatly appreciate the warm welcome from this group. We look forward to participating in this research and contributing to the scientific community in any possible way.

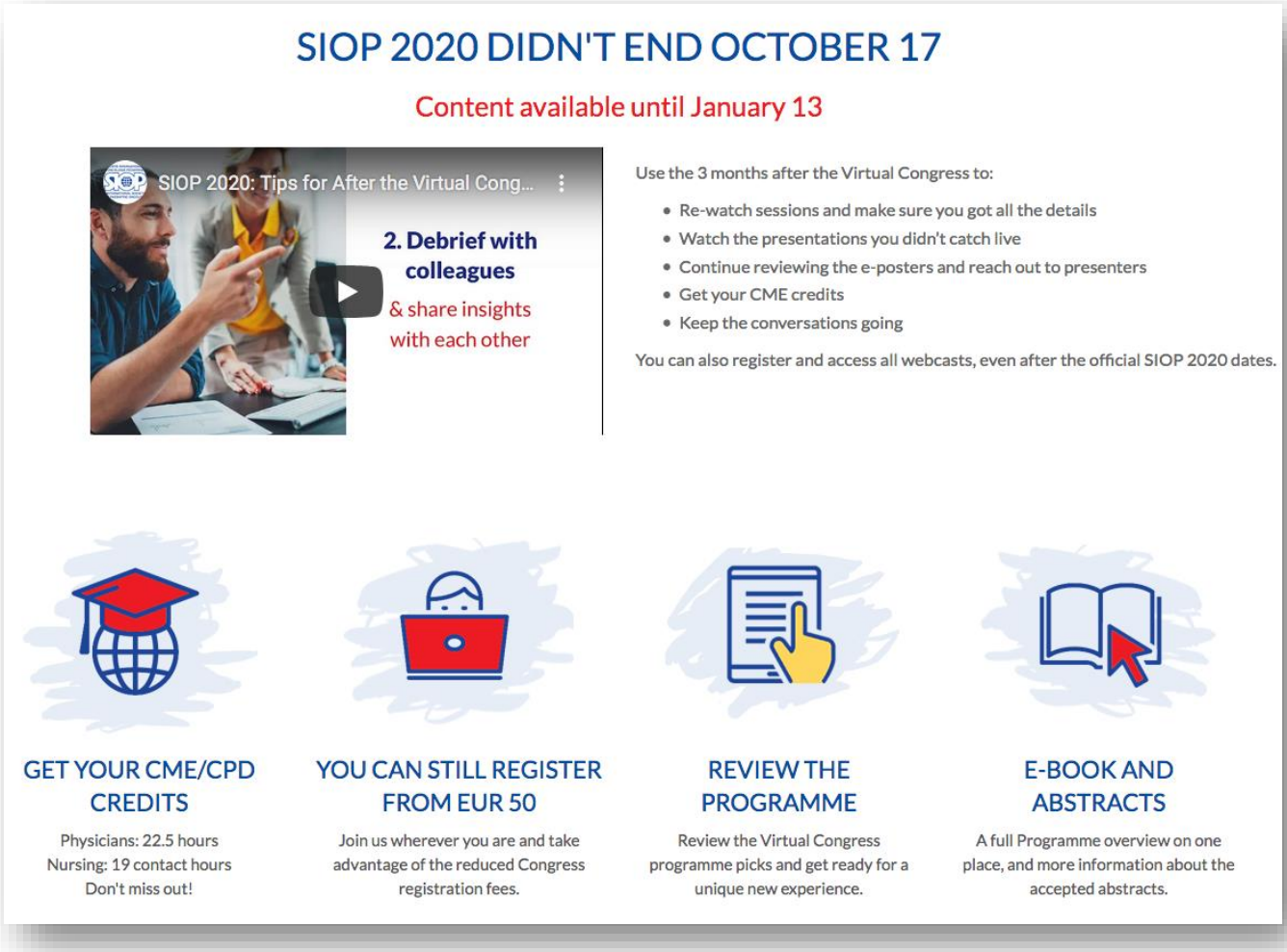
Report on the SIOP 2020 Virtual Congress

by Kathy Pritchard-Jones, SIOP President - https://siop-congress.org/

The SIOP 2020 congress was originally scheduled to be held in Ottawa, Canada, in the autumn of 2020. The switch to a completely 'virtual' on-line format, mandated by the COVID-19 pandemic, was an experiment for us all. Fortunately, the global paediatric oncology global community is very dedicated to sharing learning and open to new ways of working. 3,350 delegates embraced the opportunity to join the congress programme over 4 days of stimulating keynotes, symposia and presentation of hundreds of research talks and posters. This was a 30% increase on numbers attending SIOP 2019 in Lyon. Delegates came from 134 countries, with 40% working in low- and middle-income countries (LMICs) and many attending for the first time. Thus, SIOP 2020 has been the largest and most diverse congress to date, doubling attendance from LMICs. The SIOP Board aims to retain these benefits of the virtual congress in planning a hybrid format for SIOP 2021 in Honolulu

The session with the highest live attendance was the "BATTLE OF THE CONTINENTS -APPROACHES TO THERAPY FOR WILMS TUMOR" with Marry van den Heuvel-Eibrink defending the pre-operative chemotherapy SIOP corner and Jeff Dome defending the immediate surgery COG corner! Over two thousand delegates tuned in to hear this debate from all over the globe. Renal tumour research presentations were prominent in the IPSO and PROS programmes as well as featuring in the symposium on the Global Initiative on Childhood Cancers – where Wilms tumour is one of the six focus tumours for improvement. It was very pleasing to hear the presentation from Vivian Paintsil from Ghana representing the Collaborative WT Africa group, about improvements in event-free survival rates to 50% across six centres in sub-Saharan Africa. There was large reduction (approx. halving) of abandonment of treatment rates down to 12% and deaths during therapy down to 13%. Whilst there is still some way to go to achieve the WHO target of at least 60% survival, they are well on the way, using an adapted treatment regimen based on the SIOP-RTSG practice.

Of high relevance to the UMBRELLA protocol was the presentation by Jesper Brok on THE CLINICAL IMPACT OF OBSERVER VARIABILITY IN LUNG NODULE CLASSIFICATION IN CHILDREN WITH WILMS TUMOUR. You can see this and all the other congress content online through to Jan 15th, 2021 (you have to be a paid delegate to log in). Please do avail yourselves of this opportunity to review the congress content at your leisure. It is still possible to register.



SIOP Congress in Honolulu, Hawaii, 2021

https://2021.siop-congress.org/

Hopefully this congress will take place in presence! Follow: https://2021.siop-congress.org/

SIOP-Europe Annual Meeting in Valencia, Spain, 2021

https://www.siopeurope.eu

SIOP Europe, alongside CCI Europe, made the difficult decision to postpone the **2nd SIOP Europe Annual Meeting**, which was scheduled to take place on 4-8 May 2020 (Valencia, Spain) due to the Coronavirus (COVID-19) pandemic.

The new dates: 26-30 April 2021 (Valencia, Spain)!

The Annual Meeting will once again be held in partnership with CCI Europe, who will be holding their 11th 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.

We hope that the conference can take place in Valencia. Depending on the Covid-19 pandemic this will not be possible, and a virtual conference will be set up. Please keep updated:

www.siopeurope.eu | Twitter: **#SIOPEurope21**

SIOP-RTSG Meeting, Rio de Janeiro, Brazil, 2020

By Joaquim Caetano de Aguirre Neto and Beatriz de Camargo (local organizers)

It was a great pleasure to host the last for a long period a *face-to-face* meeting in March 2020 (11-13) in Rio de Janeiro, RJ, at Hotel Vila Gale, Lapa.

At the last moment before the meeting the WHO recognized the COVID-19 as pandemic, and unfortunately many colleagues could not travel to attend this meeting. We organized a hybrid format including a virtual ZOOM meeting. The meeting was not cancelled because at that time the Brazilian government imposed no restrictions for meeting with less than 100 participants.

The meeting had the participation of 11 countries with 85 participants: 59 from Brazil, 10 from The Netherlands, 2 from France, 3 from Germany, 4 from United Kingdom, 2 from Russia, 1 from Qatar, 1 from Argentina, 1 Sweden, 1 from Norway, 1 from Japan, plus 10 colleagues who participated via ZOOM platform during the 3 days.

Two days before a SIOP Pathology Panel review was organized by Isabella Werneck (Brazilian national reference pathology). On March 11h, the Steering Committee meeting was held thought virtual Zoom with 7 members plus 8 locally.

The meeting started on March 12 with welcome from Beatriz and an overview of UMBRELLA Study from Marry. There were six parallels sessions: stage IV, surgery, radiotherapy, radiology, relapse and the first Brazilian Parents meeting. There was also a session of difficult cases discussion with a lot of participation.

The large participation of Brazilian colleagues from all regions stimulated the cooperation and increase the accrual of patients on UMBRELLA protocol from Brazil.

The Brazilian committee would like to thank all the colleagues who attended in a difficult time of life and contributed to a very successful meeting.

10th International Paediatric Renal Tumour Biology Virtual Meeting, September 24th, 2020

Even if some of us hoped that the pandemic would end earlier and we could all gather in sunny Marseille at a wonderful harbor location, there was no chance to hold the 10th International Renal Tumor Biology Meeting in Marseille as planned. Nevertheless, there was uniform consent that we should have a smaller interim meeting in the format of a video conference to update everyone on the latest developments in various fast-growing fields – and Marseille is still waiting for us! Fortunately, the supporters of the Marseille meeting as well as the Princess Maxima Center and the COG were able to provide funds to organize and run the online event. A core team of Manfred Gessler, Marry van den Heuvel and Arnauld Verschuur for SIOP-RTSG and Jim Geller, Conrad Fernandez and Elizabeth Mullen for COG took over the planning.

Early on it became clear that a complete program with posters and short talks would be overambitious for our online meeting. The organizers from SIOP-RTSG and COG instead decided to have a series of plenary talks that covered just three major topics: liquid biopsies, tumor models and the results from large scale genetic analyses, each followed by round table discussions. This approach proved to be interesting to many of us and we had the unanticipated number of 255 registrants. The duration of the meeting was shortened to seven hours with intermittent breaks that limited Zoom fatigue and helped participants to stay alert despite the long hours into the evening in Europe or the early wake-up calls for others, especially on the American west coast. For ease of communications and smooth transitions Manfred Gessler chaired the entire meeting together with Jenny Wegert.

Liquid Biopsies – a new buzzword in oncology: The first session was devoted to the analysis of liquid biopsies, i.e. the opportunity to gain information on a tumor by just drawing a blood samples instead of a physical biopsy with all its possible complications or its limitations in case of unreachable or distantly spread tumor sites. The three speakers, Gudrun Schleiermacher (Paris), Bram de Wilde (Ghent)and Brian Crompton (Boston) presented several cases studies that illustrated the possible scenarios for its use - from individual ddPCR or low-coverage genome sequencing to panel or whole exome and genome sequencing as well as global methylation analysis. Issues like sensitivity, bioinformatics challenges and detection limits were discussed as well as the timing of individual analyses, either prospectively, at time of diagnosis or during treatment and later follow-up. There is a broad range of genetic alterations that are amenable to such tests, be it the high sensitivity detection of individual mutations or copy number profiles, global unbiased mutation screening, or epigenetic analyses. More specialized applications like RNA analyses or urine testing were only briefly touched, but it became clear that there will be multiple different types of assays that will have to be tailored to the individual situation.

And we still have to learn a lot about the factors that influence the contribution of tumor-derived DNA to the pool of circulating DNA and how different tumor cell types, regional differences or response to therapy may affect their ratio. Even if such tests have not yet made it into broader clinical routine, it became apparent that they have enormous potential to strongly influence diagnostic yield and shape future treatment strategies.

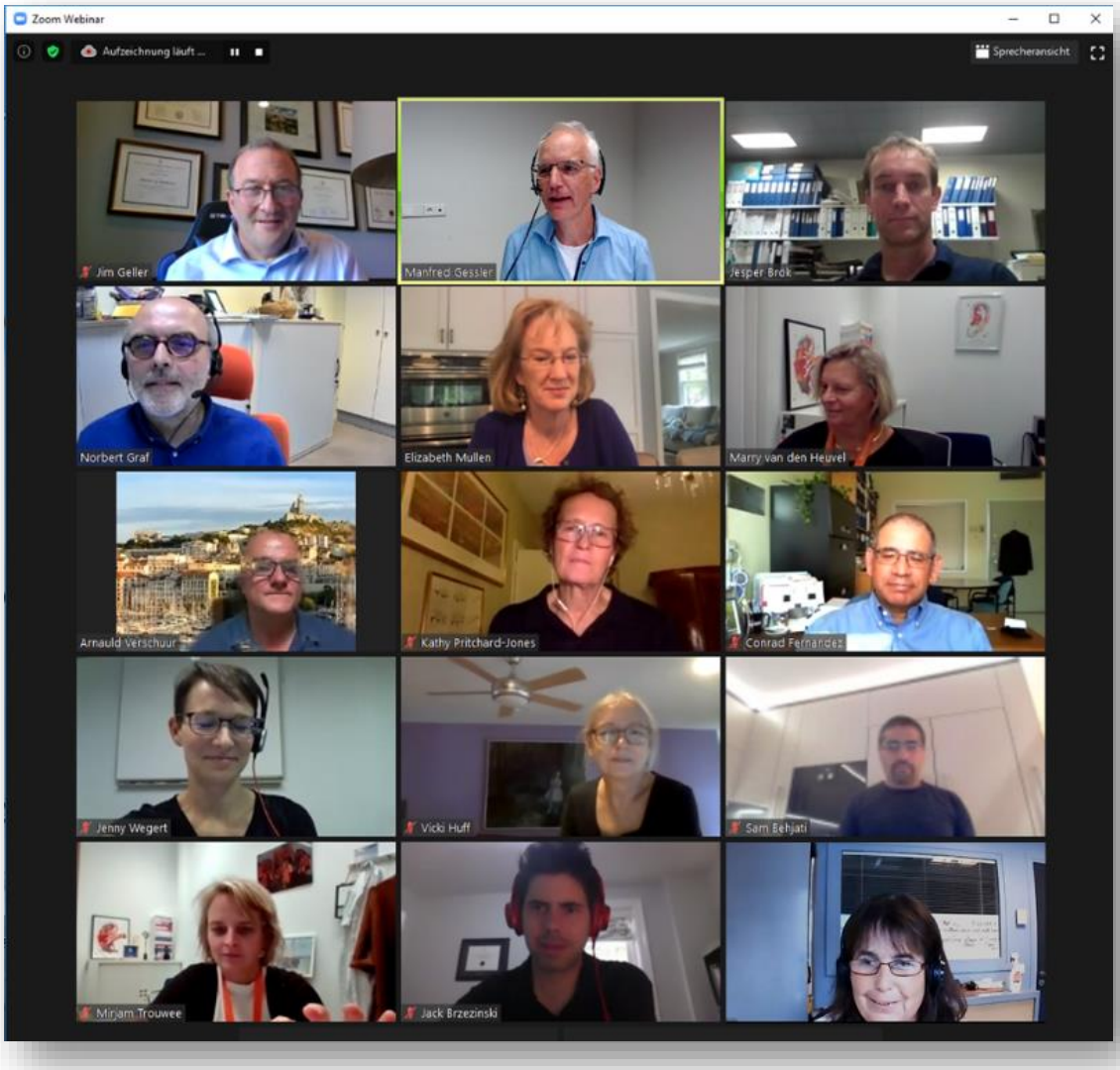
Models for Wilms tumor: The session on tumor models covered all levels from genetically engineered mice to xenografts and organoids as proxies for functional analyses and drug screening. Vicky Huff (Houston) provided an overview on almost three decades of knockout mouse models as surrogates for human Wilms tumors. While this work by many labs has led to great new insight into developmental biology of the kidney, it is also clear that this approach cannot provide easy answers but needs detailed analyses with multiple cre-lines to hit the relevant cell types and developmental time points. Andrew Murphy (Memphis) presented data on a new resource of 45 xenografts that represent the biological and clinical heterogeneity of Wilms tumors. Despite a general gain in blastema, there was a good correlation between primary and xenograft samples in histology and therapeutic response, which may especially benefit relapse cases. An even faster route to drug testing may be available through organoids as presented by Jarno Drost (Utrecht). The best example was rhabdoid tumors that exhibited exquisite sensitivity towards mTOR and HDAC inhibition, which could be unraveled by a novel screening approach aiming at differentiation therapy.

How does a normal kidney develop? Nils Lindstrom (Los Angeles), our guest speaker, presented a large volume of single cell analyses and spatial imaging data that led to a revised model of nephrogenesis with stepwise definition of precursors for cap mesenchyme-derived cell types in the maturing kidney. He described in detail the almost stereotypic waves of gene expression and cell fate determination that lead from renal vesicle to S-shaped bodies and he could describe the path used for each cell type and integrate this with protein profiles and 3D-location in unprecedented detail.

Mutation screening: The final session on large scale screening of Wilms tumors highlighted our current understanding of the genetic basis of Wilms tumors and their cellular diversity and evolutionary history. Sam Behjati (Cambridge) described how he could reconstruct the development of tumors based on mosaic mutations that uncover shared common ancestors in case of heterogeneous or especially bilateral cases supporting a model of clonal nephrogenesis with very early selection of tumor precursors that also produce normal kidney tissue. The 11p15 epigenetic state seems to be important in this respect. This methylation status was also in the center of the work presented by Jack Brzezinski (Toronto), who proposed a new classification of Wilms tumors based on *H19* and *KCNQ1* methylation profiles. Interestingly, these subgroups differed in relevant clinical parameters like recurrence risk or bilateral disease. RNA expression seems to further split one of the groups yielding three classes with partly distinct early and late genetic changes. The session also included brief updates on current large-scale sequencing efforts under way in the US (V. Huff), France (G. Schleiermacher) and the UK (K. Pritchard-Jones). These will provide us with a great resource to further develop genetic classifications and improved biomarkers and targeting options.

The outlook: The ensuing broader discussion on "Implications for renal tumor biology studies" led by Jim Geller together with Elizabeth Mullen, Kathy Pritchard-Jones, Jesper Brok and Norbert Graf put the molecular work with fascinating new insights into Wilms tumor biology into perspective of clinical reality and needs. It highlighted the challenges of translation, but also showed that we are on a good track to provide paths to incorporate these novel findings into future clinical trials. Nevertheless, questions of immune response or the microenvironment and tumor-host interactions are rarely taken up and biological excitement may not always be relevant for the majority of patients.

The meeting proved to be very interesting and stimulating for basic scientists and clinicians alike, highlighting new avenues for future work, opportunities to be chased and new options for enhanced international collaboration. Marry van den Heuvel, who contributed a lot in the background with her technical team to smoothly run the event, closed the meeting. It was then left to Arnauld Verschuur to invite everyone to next years "real" meeting that will hopefully be possible in person in Marseille, France from September 22-24, 2021. Please check the SIOP-RTSG web site or your E-Mail account for future announcements and we will expect to see you there!



Closure of the meeting with many of the key contributors on and behind the screens.

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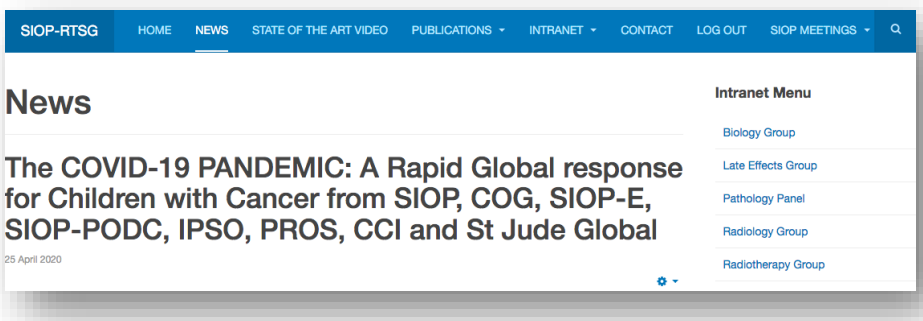
Our Website

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

23rdh to 26th of March, 2021	Chicago, IL, United States	COG Spring Group Meeting (invitation only)
To be announced 2021	Virtual Format	AACR Annual Meeting 2021
26th to 30th of April 2021	Valencia, Spain or virtual	2nd Annual SIOP Europe Meeting
3rd to 7th of June 2021	Chicago, IL, United States	ASCO Annual Meeting 2021
24th to 25th of June 2021	Utrecht, The Netherlands	SIOP-RTSG Committee Meeting
22nd to 24th of September 2021	Marseille, France	11th Int. Pediatric Renal Tumour Biology Conference
28th September to 1st of October 2021	New Orleans, LA United States	COG Fall Group Meeting (invitation only)
21st to 24th of October 2021	Honolulu, Hawaii, USA	53rd Congress of SIOP

Impressum

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