Since 1971 the International Society of Paediatric Oncology is running prospective clinical trials for nephroblastoma. The number of participating countries, centres and registered patients in these trials and studies did steadily increase over time as shown here:

All these activities over the last 40+ years resulted in better outcomes of patients due to individual risk factors. Nowadays around 90% of patients with Wilms tumour survive, but a number of them still relapse and die. We do know many tumour related risk factors, but we need to find additional molecular markers for better stratification of patients. In addition, there are still differences in outcome depending on the country where a child is diagnosed and treated. Therefore, our new UMBRELLA Study addresses these questions in detail and is aiming to offer all patients with kidney tumours the same standardized high quality diagnostics and treatment, independent of the tumour type, the socio-economic status or the geographic region where the patient is living.

We are proud that up to now most European countries and many countries from other continents have confirmed that they will be participating in the UMBRELLA Study, making it a worldwide study.

Norbert Graf  
Mary van den Heuvel-Eibrink  
Gordan Vujanic
UMBRELLA Study
By Norbert Graf

After the end of SIOP 2001 we developed a new protocol for the standardized diagnosis and treatment of kidney cancers in childhood, adolescents and young adults. Given the relative rarity of paediatric renal tumours and in particular rare subgroups, our previous studies demonstrated that it is necessary to recruit as many patients as possible at a population level. Since SIOP 93-01 SIOP-RTSG registered nearly 8,000 patients with a renal tumour from 261 centres across 28 countries. All of them have been treated according to consensus European trials and protocols. This has resulted in improved risk stratification and adjusted treatment recommendations for most renal tumours. This success story needs to continue with the upcoming UMBRELLA Study by finding new risk factors for better diagnosis and treatment and thus improving the outcome of patients with nephroblastoma and other kidney cancers.

The hallmark of the SIOP RTSG approach is the preoperative chemotherapy (Vincristine and Actinomycin-D in localized and with the addition of Doxorubicin in metastatic disease) without preceding mandatory histological assessment. As we all know, this has the clear evidence-based benefit of down staging tumours, thereby sparing survivors the late effects of doxorubicin or radiotherapy by around 20% compared to patients treated with immediate surgery. Nevertheless, this approach carries the risk of misdiagnosis (< 5%), as currently the so-called non-Wilms tumours cannot be identified by standard radiology or existing discriminating biomarker assessment.

As a consequence, the current SIOP 2016 integrated research and diagnostic UMBRELLA protocol (part A) serves as an entry for including all children with a renal tumour in Europe and other participating centres in the SIOP-RTSG. Subsequently, treatment of all renal tumours is recommended according to the UMBRELLA treatment guidelines (part B), which provides treatment strategies for all nephroblastoma patients and all children with other renal tumours. These recommendations are mainly based on the results from the previous SIOP and COG trials. According to the results of the recently closed SIOP 2001 trial all children with localized stage II and III intermediate risk tumours will receive no doxorubicin in the postoperative chemotherapy anymore as the new standard of care. The detailed clinical treatment guidelines and follow up protocols for all renal tumours in children and young adults are available to all participating centres.

For nephroblastoma treatment guidelines are according to SIOP 2001 to allow a prospective validation of prognostic biomarkers like 1q gain and others. Despite the fact that the overall outcome of patients with nephroblastoma is excellent, there are still subgroups of patients with unacceptable numbers of relapses and deaths. Without the addition of biological markers and imaging features as stratification parameters, further improvement of outcome cannot be gained. Thus, further knowledge needs to be generated from imaging, pathological and biological studies. In the UMBRELLA Study the smooth sharing and joining of this data is mandatory as well as refining logistics for the availability of high quality data and information from reference centres of radiology, pathology, surgery and radiotherapy in due time. New ways of data analysis will be established to select those biomarkers and imaging features that will have the highest impact as new stratification parameters for subsequent randomized clinical trials. The provision of an integrated IT-infrastructure as well as the inclusion of bio-informaticians in this process is mandatory.

The UMBRELLA Study is already approved by the ethical committee of the ‘Ärztekammer des Saarlandes’ in Germany, has received an EUDRACT number (2016-004180-39) and a Universal Trial Number (U1111-1196-3034). These numbers are given despite the fact that the UMBRELLA Study is an observational study not asking any treatment question. Sponsor of UMBRELLA is the Saarland University, Germany (HOM-01-Klin-2017). Contracts with participating countries are under way. The protocol is available for participating centres under http://www.siot-rtsg.eu/ in the Intranet. Financial issues are still needed to be solved.

Every hospital that wants to participate in the SIOP 2016 UMBRELLA Study needs to be a member of a National Group registered in SIOP-RTSG or - in the absence of a National Group - a single centre adhering to the ‘Structures and Standards’ given by the SIOP-RTSG. Each participating centre has to enroll every patient with a renal tumour into this study and provide information about responsible persons (paediatric oncolgist, radiologist, pathologist, radiotherapist, surgeon) dealing with these patients and all of them have to sign that they do adhere to the UMBRELLA Study and that they provide all requested material (imaging, pathology, biomaterial) and data.
Minimal requirements for participating as a partner institution are

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

Countries that can only meet criteria 1 and 2, are welcome to register patients and to use the therapeutic guidelines. For each patient quality criteria are collected for further analysis. Central pathology review is mandatory for inclusion in any kind of analysis and it should be, preferably, rapid central pathology review. Further analyses will not be possible due to selection bias if a central radiology review of images is not done.

Requirements for enrolment in the final analysis of research questions

1. In all countries with functional biobanking structures the submission of at least one sample of frozen tissue with corresponding control (blood or adjacent normal kidney in case of nephrectomy) is mandatory. In countries that do not yet have this infrastructure the minimal requirement is the submission of a representative paraffin block of tumour and matching normal kidney for biology studies. However, it is strongly recommended that biobanking is organized on a national level (fresh frozen tumour tissue as well as normal renal tissue, peripheral blood and urine, including also blood/serum from parents). Centres from countries with existing biobanking structures will provide support to guarantee the collection of materials at the best level possible.
2. Abdominal DWI-MRI at diagnosis and after preoperative chemotherapy

Inclusion criteria

All children, adolescents or young adults with a primary or relapsed renal tumour diagnosed in a participating SIOP-RTSG centre are eligible for inclusion in the SIOP 2016 UMBRELLA Study. All registered and participating centres in the SIOP-RTSG Study group have to enroll all their patients with renal tumours into this study, if the patient or the parent or the legal representative (guardian) gives informed consent. Consent needs to be given separately for the enrolment in the study, the sharing of data and the biological studies related to the protocol. The inclusion of patients is independent of the histology of the renal tumour, the age of the patient (except for RCC patients: <18 years old) or the country of residence. All participating centres agree to be compliant with the study and to provide all requested material including imaging studies and biomaterial, data and other necessary information of all their enrolled patients. This includes also follow-up information on at least a yearly basis. Recruitment of patients is aimed to be complete in all participating centres with the provision of complete data sets and requested imaging and biomaterial.

Exclusion criteria

The only exclusion criterion is missing informed consent. Patients who do not give or whose parents or guardians do not give consent for inclusion in the UMBRELLA Study cannot be registered. As there are different consents for participation in the clinical and the biological part of the UMBRELLA Study patients can be potentially registered if there is consent given for the clinical part only and not the biological part of the study. Each country in accordance with local regulations rules will provide consent forms in their language.

Website: siop-rtsg.eu

For further details, please visit our website at http://www.siop-rtsg.eu/. Information will also be given via mails on a regular basis. Invitations to our yearly meetings are provided to all members of SIOP-RTSG for updating news.
With the start of the new UMBRELLA Study, efforts to enhance biobanking and to develop clinically relevant biomarkers have now become central cornerstones for future success. While the COG protocols already include molecular markers in clinical decision-making, the results from our prior SIOP-RTGS studies are encouraging, but not yet definitive. With the now even larger community of participating countries, we expect to collect sufficient materials for definitive studies. These will be aimed at clarifying the clinical utility of molecular data within the SIOP Study and to demonstrate our ability to generate molecular diagnostic data in a short time frame if needed.

**Primary aim 1q status**

In our recent publication by Chagtai et al. [1], we analyzed 586 Wilms tumour cases, of which 28% showed gain of chromosome 1q. This marker was associated with lower 5yr-EFS and OS. In multivariable analysis 1q gain was still significantly associated with lower EFS after adjustment for several parameters like 1p and 16q loss, sex, stage, age, and histologic risk group. However, for OS the adverse effect no longer reached statistical significance, likely due to low numbers. Nevertheless, comparison with other markers like LOH 1p & 16q, or loss of 2p (MYCN) or 17p (TP53) showed that gain of 1q still is a promising biomarker candidate. In the COG Study with upfront surgery, 1q gain is now part of clinical risk stratification. Therefore, the goal of the new UMBRELLA Study is to provide a larger cohort of tumours to prospectively study the independent adverse effect of 1q gain for patients treated according to the SIOP Study under conditions where residual blastemal volume is now also scored as an additional clinical marker.

**How to test for 1q gain?**

There is no consensus yet on the best approach to for testing 1q alterations. While numerous techniques have been shown to work reliably in the past, there are vast differences in cost and labour. Our prior study was successfully performed by MLPA analysis [1], but the limited number of probes only leaves room for a small set or targets. SNP arrays on the other hand will provide a much better resolution along each chromosome to identify critical subregions, and it provides a genome-wide view of many loci of interest, including copy number neutral LOH. Lastly, the falling cost of genome sequencing may allow low-level coverage to become an alternative. Since we need large numbers of samples with follow-up data at hand to evaluate the clinical relevance of 1q gain, we should still take our time to see which option turns out to be the best in terms of expense and information obtained. However, we have to collect all tumours in the meantime.

So please make sure that every tumour can be included in our biobanks in every country. For those with limited resources for testing, collection is equally important. We will ensure that all cases can be included via the larger centres with appropriate funding that can perform these analyses.

**Biobanking must include frozen materials**

Although more tedious, time-consuming and costly, it is very important to collect not only formalin-fixed materials for histopathology, but also snap-frozen samples for molecular analyses. While techniques to use formalin-fixed paraffin-embedded (FFPE) material are improving, this will not match the breadth and quality of analyses that are possible with fresh-frozen materials stored at ~80 °C or below. Thus, it will be of utmost importance to reach a comprehensive coverage of all tumours as high quality frozen materials for future studies. As hypoxia and lack of perfusion strongly affects gene expression patterns, it is critical to achieve fast freezing of tumour samples and to document the time needed.
Capture heterogeneity!

From numerous studies, it is becoming clear that Wilms tumours can be genetically heterogeneous [2, 3]. There are probably several driver alterations that occur very early during malignant transformation and these are present in the vast majority of tumour cells. On the other hand, some genetic alterations can be present in certain areas of a tumour only, while sparing others. Singular cases have been reported for probably many of the genomic changes that are seen in Wilms tumours. For certain alterations, this seems to be a more frequent scenario, however. Among these are e.g. gain of 1q, WTX mutations or TP53 mutations.

Currently we do not know if this reflects tumour evolution towards a more malignant form. Some changes could also be attributable to selection pressure due to chemotherapy. Nevertheless, it will be important to assess this diversity of cell types in tumours and to test if this forms a pool of clones for selection imposed by various means. These might be our therapy, intrinsic tumour growth patterns and nutrient supply or evasion from the immune system.

To capture this genetic pool of variants, it is critical to collect multiple samples from each tumour [2]. While it is important for the pathologist to identify the primary biopsy as the one that best characterizes a given tumour and submit this to the biobank, additional samples that reflect the macro- and microscopic variability are of utmost importance to provide a complete picture of a given tumour.

Furthermore, it is very important to collect both FFPE and frozen material at tumour recurrence [3]. In fact, comparison of genetic alterations present in primary and recurrent tumours may help to identify mutations that promote relapse and thus define novel therapeutic targets.

A wealth of new Wilms tumour genes

While culprit genetic changes were missing in a large fraction of Wilms tumours for many years, the recent next-generation sequencing projects, especially of the SIOP and COG cohorts have identified a number of additional potential driver genes that may explain the genetic basis of tumour formation in most cases [4, 5]. This approach has now been extended in the just published follow-up by the COG Study, based on a validation cohort of 651 Wilms tumours [6]. This effort provided a figure of 68% of tumours carrying mutations predicted to be damaging, with the remainder expected to have critical copy number alterations or other rare mutations.

While these novel Wilms tumour genes currently still lack correlation with clinical features, the link of TP53 mutations and anaplasia in Wilms tumours has been strengthened [7-9]. The presence of TP53 mutation in cases that lack typical features of anaplasia indicates that additional testing, e.g. by p53 immunohistochemistry may be helpful in future to better classify tumours.

Again, efficient biobanking will foster future research to explore the clinical relevance of all these novel Wilms tumour genes and may help to uncover vulnerabilities of tumours that can be addressed by targeted therapies.

Liquid biopsies – the future integrative diagnostics?

For multiple types of cancer, characterization of genetic alterations by liquid biopsies has proven to be highly informative - and sensitive as well. The non-invasive nature (well, still a blood draw for kids, and urine samples) makes them ideal for upfront diagnostics, longitudinal monitoring of response or tumour evolution and for follow-up screening to capture relapses.
For pediatric kidney tumours, this approach holds great potential. Areas to utilize such test would be to aid in (1) the detection of non-Wilms tumours preoperative or perhaps even before chemotherapy, (2) monitoring of chemotherapy response, (3) the chance to obtain a global and integrated picture of genomic alterations in heterogeneous tumours and finally (4) early detection of relapse. It is certainly early days for such concepts, but to turn such possibilities into clinical options we need a thorough program of testing and comparing liquid biopsy material and corresponding tumour samples. While this will certainly require appropriate funding, a key step for future analysis will be to collect blood plasma samples starting immediately.

In addition, we ask for blood samples drawn in PAXgene tubes. These specifically permit the analysis of microRNAs that are deregulated in many cancer types, including WT. Previously, treatment-independent miRNA signatures have been found in the blood of WT patients [10, 11]. Specific miRNAs show a significant upregulation in the blastemal and the regressive subtype and miRNAs regulating epithelial to mesenchymal transition are deregulated in the blastemal subtype.

Blood plasma and blood PAXgene sampling to test these alterations can easily be done during the initial visit and during follow-up and it will be an important add-on for the UMBRELLA biobanking.

References
Central pathology review (CPR) has been part of all SIOP Trials and Studies since 1971, but only since 2001 Trial in some parts of the Trial it was done as rapid CPR. The reason for introducing “real time” or “rapid” CPR was based on the results of previous Trials and Studies which showed that a significant number of mis-diagnosed and/or mis-staged cases was consistently around 20-25%, but since CPR was done retrospectively, it had no influence on treatment.

Although rather challenging, and requiring a good organisation and dedication of people collaborating in the system of rapid CPR, it proved to be possible to deliver and has been working very successfully, with 97% of cases in the UK, for example, submitted for rapid CPR, enabling treatment of children to be modified in cases with discrepancies between the institutional pathologists and central pathology reviewer.

In the UMBRELLA Study, rapid CPR is mandatory, and all participating countries and centres should organise themselves and participate according to the scheme outlined in the Protocol. Briefly, there will be the following National/Regional Pathology Panels which will be delivering rapid CPR:

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
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<tbody>
<tr>
<td>Naglaa El Kinaai</td>
<td>Egypt</td>
</tr>
<tr>
<td>Aurore Coulomb-L’Hermine</td>
<td>France</td>
</tr>
<tr>
<td>Christian Vokuhl</td>
<td>Germany</td>
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<tr>
<td>Paola Collini</td>
<td>Italy</td>
</tr>
<tr>
<td>Yukichi Tanaka / Hajime Okita</td>
<td>Japan</td>
</tr>
<tr>
<td>Ellen D’Hooghe</td>
<td>Northern European countries (Scandinavian and Baltic)</td>
</tr>
<tr>
<td>Jozef Kobos</td>
<td>Poland</td>
</tr>
<tr>
<td>Isabela Werneck da Cuhna</td>
<td>South America</td>
</tr>
<tr>
<td>Enrique de Alava</td>
<td>Spain</td>
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<tr>
<td>Ronald de Krijger</td>
<td>The Netherlands/Belgium</td>
</tr>
<tr>
<td>Gordan Vujanic</td>
<td>U.K.</td>
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<tr>
<td>Gordan Vujanic</td>
<td>All other countries</td>
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Since the time frame is very tight - 21 days between the last dose of preoperative chemotherapy and the first dose of postoperative chemotherapy, it is important to have the cases sent promptly, without any delay, even if the final report by the institutional pathologist is not fully ready, since it can be emailed to the National/Regional Pathology Panel while the slides are ‘travelling’ to them. The National/Regional Pathology Panel should communicate their opinion within 1-3 days (in the majority of cases). All cases seen by the National/Regional Panels will be later reviewed by the SIOP Pathology Panel at the meetings where the Chairs of the National/Regional Panels will be invited to participate.

We are hoping that the countries where the rapid CPR has been going on for years will continue to do it successfully in the UMBRELLA Study, but even more, that the countries which are new to this system will embrace it and very quickly appreciate its benefits, first of all for the patients, but also for the pathologists and oncologists.
Central Radiology Review: A major step forward!

By Anne Smets

Centralized radiology review (CRR) is one of the major steps forward in the standardization of imaging interpretation and consequently an improvement of the stratification of patients in the UMBRELLA Study.

CRR consists of a “real time” or “rapid” (within 96 hours, weekends and national holidays excluded) review of the imaging studies by an independent radiologist with expertise in renal tumours in children. Within the UMBRELLA Study CRR has been organized on a national basis: every participating country has appointed a referent radiologist who will review the imaging studies of all renal tumour patients in his/her country. For countries where this particular expertise is not available, a request can be made for CRR by the RTSG expert radiology panel. The panel will also carry out independent review for patients treated in the referent radiologists’ centre, provide expert opinion for selected difficult cases and perform quality control.

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

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

This double reading will increase the quality of interpretation of the imaging studies and thus the correctness of the assessment of the status at diagnosis and of treatment response. The Study also aims at improving the technical quality of the imaging studies by providing detailed radiological guidelines. Furthermore, the referent radiologist and the radiology panel are available for guidance, for answering questions related to imaging in general and to give feedback on the quality of imaging studies.

Teamwork is required for all these efforts to work: if paediatric oncologists include and engage the radiologists in their hospital, they will automatically become aware of the radiological issues, they can discuss with their radiographers how to implement the imaging guidelines in their local routine and they will find their way to the referent radiologist and the RTSG radiology panel for advice and support.
SIOP UMBRELLA Data Management Infrastructure

By Harm van Tinteren

For the UMBRELLA Study, not only a complete new protocol has been written including the latest insights in the field of diagnostics and treatment of Wilms’ tumours, but also data management will also be completely redesigned.

For previous SIOP-RTSG trials and studies, data collection, processing and analysis were complex and time consuming. At a local level, paper Case Record Forms (CRFs) were completed and sent to national data centres by mail. Then, the information from CRFs had to be entered into a database. If any inconsistencies or incomplete data were observed (based on face value) queries had to be sent back to the local hospitals. Corrected and new forms were to be sent to the national centre where they were processed again. On a yearly basis, data from five different (national) sources, sometimes based on slightly different forms or different versions of forms, including different variable names or codes had to be merged into one single master file. The individual files were sent in different formats using different methods to cope with the increasing sizes. Usually, due to the time constrains, it was difficult or impossible to communicate about potential inconsistencies or incomplete data that appeared while analysing. Realizing this, it may almost sound like a miracle that we successfully completed and published two randomized controlled trials. However, luckily the whole chain of people involved consisted of well-motivated and dedicated professionals at all levels with an overdose of perseverance and devotion.

The start of the UMBRELLA Study however gives the opportunity to introduce a more up-to-date and sophisticated method of data collection. An electronic CRF will replace the paper CRFs. No need to explain that especially in an international and multicentric environment this potentially bears a great deal of advantages. Data will be collected uniformly, checked for inconsistencies and incompleteness partly automatically and in principle full data will be available at any time. The progress of data entry can be followed and supported centrally by a few dedicated data managers. Inconsistencies of incompleteness discovered by the data managers can be queried regularly from within the system. The system for eCRFs that has been selected is called ALEA. ALEA started as an initiative in the late 80’s when the MRC (UK), the EORTC and the Netherlands Cancer Institute (NKI, NL) were in need for randomization and registration software for subsequent grants from the European Commission it clinical trials. Later, in 2004 with the support of two was further developed by the NKI into a complete eCRF-system. Currently development of the system takes place at FormsVision, a ‘spin-off’ of the NKI. The system is now in use for clinical trials worldwide. An important aspect of ALEA is that it is based on the CDISC standard ODM (Operational Data Model). CDISC is a global, non-profit charitable organization that develops data standards to streamline clinical research. ODM is the standard they developed for representing clinical trials data. It provides the structure according to which clinical data from a trial can be organized consistently and efficiently. Statistical programs such as SAS have procedures developed that can directly process the data according to this model.

In the past months, with the help of Janna Hol, Marry van den Heuvel-Eibrink, Norbert Graf and other members of the RTSG Steering Committee and the eCRF team of the NKI, the paper CRFs of the SIOP 2001 Study have been revised according to the new protocol. The new CRFs were then evaluated and updated by the chairs of the subcommittees of SIOP RTSG. The paper CRFs have been translated and programmed into electronic CRFs. One of the many useful phenomena of eCRFs compared to paper CRFs is that parts of a form can be hidden for users if not applicable and appearing or even extended (endlessly) when necessary or relevant. Also, the eCRFs went through a series of interactive validation phases among the different disciplines and the eCRF programmers. Finally, a series of test patients have been entered to validate and verify the complete system. So far, the eCRFs are ready to be used in practice.

However, there are still a number of steps and issues to be solved. Some of them are very practical. Patients can only be registered by or on behalf of a clinician. Local data managers can enter and access patients from a single hospital and central data managers can enter and access patients from different hospitals. Monitors may get ‘read’ access and options to put queries without being able to modify data. To obtain any access to the system, a name, e-mail address, affiliation and ‘role’ (physician, data manager, monitor, etc.) is mandatory. Centres that would like to start entering patients into the system need to provide these names and addresses to the central data centre (SIOP office) at the Princes Maxima Centre (PMC) in the Netherlands.
Issues that still need to be resolved have directly or indirectly to do with the challenges for getting compliant with the European Union’s General Data Protection Regulation (GDPR) that will be in effect as of May 2018. This regulation basically involves some new and stringent rules for collecting and storing any information related to a natural person or ‘Data Subject’ that can be used to directly or indirectly identify the person. For the eCRF system of UMBRELLA it means that we have to think carefully what data are allowed to be collected on patients (children!). In the Netherlands we are not allowed to collect the full date of birth. However, in children the exact age is by definition very important information. The rules and solutions for implementing the GDPR in the Netherlands may be (slightly) different in other countries. At the NKI we are currently investigating technical solutions for the eCRF that may guarantee compliance with the rules and we will approach the other members (e.g. countries) to verify whether our solutions are valid and supported.

Dealing with diagnostic images is another important module. Several technical solutions with different pros and cons are available and currently being evaluated. However, most solutions involve storage of a substantial amount of data and most importantly, the data need to be stored securely without any traces that can be used to directly or indirectly identify the person.

In conclusion, a new eCRF system is in place and can be used soon. The PMC together with the NKI is preparing, in collaboration with the RTSG Steering Committee, the infrastructure for giving full service to the system including trial management and monitoring for its users.
Czech Republic

By Vera Bajciova

In the Czech Republic there are about 14-16 newly diagnosed Wilms tumours and 5-6 non-Wilms tumours every year. All new patients with renal tumours will be registered in the UMBRELLA Study. Two pediatric cancer centres will participate in the UMBRELLA Study including Department of Paediatric Oncology and Haematology, Prague, and Department of Paediatric Oncology, Children’s University Hospital, Brno.

The Czech Republic participation in the UMBRELLA Study is represented by the following people:

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Biobanking is available in both centres, as well as molecular biology labs.

We would like to actively participate:

Part A:
- We are able to perform all requested biology investigations (potential biomarkers)
- For relapsed Wilms or resistant disease, patients with hereditary predisposition, unacceptable/ unexpected toxicity or non-Wilms tumour cases we are able to perform whole exome sequencing - somatic and germinal as well
- Rapid pathology/radiology review on national basis and on international panel as well

Part B: All patient with renal tumours will be registered to the study. CRFs will be fulfilled by responsible persons
Finland
By Marika Grönroos

There is an active society of paediatric hematologists / oncologists (PHO) in Finland. We meet regularly two times a year as a group, and on top of that we have a lot of research collaboration between groups and hospitals. We have five university hospitals in Finland: Helsinki, Turku, Tampere, Kuopio and Oulu. Last year at our annual meeting of PHO we decided that Finland will join the UMBRELLA Study, therefore, all of the five university hospitals will be involved. There are around 10-15 new renal tumours per year in Finland. Almost all of the patients will probably participate, since in Finland the families are generally interested in joining the studies. We have only 5.5 million inhabitants in Finland, so it is very important for us that we are able to join the international studies with more power, and the families usually understand that. All of the centres will be very committed, because today almost all paediatric cancer patients are enrolled in study protocols. We wish to get all of the paperwork finished as soon as possible, and we are all very eager to get going with the Study!

Greece
By Dimitrios Doganis

Greek RTSG is going to participate in SIOP-RTSG studies for the first time as a country whereas in the past individual departments had participated in SIOP 93-01 and SIOP 2001 studies. Greek Renal Tumours National Study Group is ready to make efforts on being compliant with any step of this process.

In Greece, 7 Oncology Departments care for approximately 20 new patients with renal tumours (up to the age of 16) per year. Pathology evaluation and radiology work-up takes place in the corresponding labs of each Oncology department. MRI, CT scan and nuclear medicine facilities are available for all Greek patients. All these participating centres agree to be fully compliant with the UMBRELLA Study protocol and have already provided information about responsible persons (paediatric oncologist, radiologist, pathologist, radiotherapist, surgeon) dealing with renal tumours patients, and all of them have signed that they do adhere to the UMBRELLA Study and that they provide all requested material and data.

Central pathology review will be done by the corresponding regional Panel whereas Central radiology, radiotherapy and surgical review have been organized on a national level in cooperation with the corresponding regional Panels. Functional biobanking structures are going to be established on a National level by October 2017. All minimally required samples as well as additional study samples (including blood, urine samples, healthy kidney tissue) shall be stored to the National Biobank upon sampling and be transferred for analysis.

Translating procedures for the informed consent forms have also already been completed and the related files in Greek language have been sent to the RTSG site to be posted. Moreover, the first approvals from the corresponding Ethics committees of some departments have been received. We are also trying to arrange issues concerning logistics including material transfer as well as finding sponsorship.

In conclusion, the Greek Renal Tumours National Study Group is almost ready to register the first patient from Greece when the UMBRELLA Study starts recruiting patients.
Hungary  
*By Gábor Ottóffy*

In Hungary we have seven paediatric oncological centres. Hopefully, all of them will be involved in the UMBRELLA Study. From May 2017 we have the ethical approval for Hungary (except two centres, but they would also like to join). I anticipate we will have about 10-15 patients annually.

We started central radiology review (CRR) and central pathology review (CPR) last year. We could achieve CRR at 40% of our patients but our infrastructure has to be improved. On the other hand I hope our pathologists will be sending all cases to Gordan Vujanic for rapid CPR from January-February 2018.

So organizing of rapid reference radiology and pathology has now priority. Collecting of biological samples does not have any value without CRR and CPR.

I hope after one year we can collect biological samples from the tumour and soon after from blood and urine also.

Latvia  
*By Marika Grūtupa*

In Latvia we have only one centre were children with oncological diseases are treated – Children’s Clinical University Hospital in Riga. It means that we need second opinion from outside of Latvia on each issue. This will be our first study as “full time” members in children hematooncology.

We have 1-3 new patients with renal tumours per year whom we are planning to involve in the SIOP-RTSG UMBRELLA Study. We have asked Anne Smets to be our reference radiologist for this study and she agreed. The reference pathologist for Latvia will be Gordan Vujanic.

We are able to do abdominal MRI and chest CT scan as standard diagnostic for each child, as well all other regular analysis encounted in the UMBRELLA Study.

In Latvia national biobanking is not yet well established and is under formation. Nevertheless, we are able to freeze tissue samples in our hospital laboratory. We are planning to collect necessary samples for biology studies, at least part of them and send them.

We are ready to provide all information for registration.

Radiotherapy is performed in adult hospital where we ensure anesthesia, if needed, and have good cooperation with them.

Currently we are in preparation process to submit the Study protocol file for Central Ethical committee approval.
SIOP-RTSG meeting, Palma de Mallorca, 2017
By Mercedes Guibelalde and Claudia Marhuenda (local organizers)

It was a great pleasure for us to have the privilege of hosting the SIOP RTSG Annual meeting. We hope you enjoyed your stay in Mallorca as much as we have enjoyed being the host of such a wonderful group that is so diverse and rich.

Thanks to all 165 delegates attending the event, representing 32 countries from five continents including Argentina, Australia, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hong Kong, Ireland, Italy, Japan, Jordan, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Russia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, UK, and USA.

And congratulations to all the presenters for his generosity sharing his talks, data and knowledge.
SIOP-RTSG meeting, Copenhagen, 2018
By Jesper Brokes, Tina Olsen, Lars Johansen and Catherine Rechnitzer (local organizers)

Copenhagen warmly welcomes you to the 2018 meeting at the IDA conference center, Kalvebods brygge 31-33, Copenhagen, Denmark.

- IDA is 10 min walk from the central station (Hovedbanegården)
- 15 min by train from Copenhagen airport (Kastrup) to the central station.

We recommend that you book your accommodation early as hotels are busy at this time of the year.

Hotels from 2 to 5 stars within short walking distance to the venue include:
- Cabinn city (2*), Wake up, Carsten Niebuhrs gade (2*, closest to the venue), DGI-byen (3*), Tivoli hotel & congress center (4*), and Copenhagen Marriott Hotel (5*).

- Meeting rooms have been reserved at the venue but please let us know if you need additional rooms (and capacity) for parallel sessions.

- Board meeting (closed) will be the 10th June at dept. 4074, Rigshospitalet, Blegdamsvej 9 (35 min from airport) followed by informal dinner. Metro (M2) from airport to Norreport St. Then there are several buses or taxi to the hospital.

For further information about venue and logistics:
jesper.sune.brok@regionh.dk or/and Catherine.Rechnitzer@regionh.dk
IDA conference center
Publications

2017

**PAEDIATRIC RENAL TUMOURS: PERSPECTIVES FROM THE SIOP-RTSG.**
Nature Reviews Urology 2017; 14(1): 3-4

**CONGENITAL MESOBlastic NEPHROMA 50 YEARS AFTER ITS RECOGNITION: A NARRATIVE REVIEW.**

**NEPHROGENIC RESTS IN WILMS TUMORS TREATED WITH PREOPERATIVE CHEMOTHERAPY: THE UK SIOP WILMS TUMOUR 2001 TRIAL EXPERIENCE**
Vujanić GM, Apps JR, Moroz V, Ceroni F, Williams RD, Sebire NJ, Pritchard-Jones K.
Pediatr Blood Cancer 20017;00:e26547. https://doi.org/10.1002/pbc.26547

**MULTIDRUG RESISTENCE TRANSPORTER PROFILE REVEALS MDR3 AS A MARKER FOR STRATIFICATION OF BLASTEMAL WILMS TUMOUR PATIENTS.**
Hontecillas-Prieto L, Garcia-Dominguez DJ, Vaca DP, Garcia-Mejias R, Marcilla D, Ramirrez-Villar GL, Saez C, de Alava E.
Oncotarget 2017; 8(7): 11173-11186

**ANAPLASTIC SARCOMAS OF THE KIDNEY ARE CHARACTERIZED BY DICE1 MUTATIONS.**
Modern Pathol 2017 Sept 1. Doi: 10.1038/modpathol.2017.100 (Epub ahead of print)

**OUTCOME OF NEPHROBLASTOMA TREATMENT ACCORDING TO THE SIOP 2001 STRATEGY AS A SINGLE INSTITUTION IN ARGENTINA.**
Cafferata C, Cacciavillano W, Galluzzo ML, Flores P, Rose A, Zubizarreta P.

**BILATERAL WILMS TUMOUR: A REVIEW OF CLINICAL AND MOLECULAR FEATRES**
Charlton J, Irtan S, Bergeron C, Pritchard-Jones K.

**RESULTS OF THE THIRD AIEOP COOPERATIVE PROTOCOL ON WILMS TUMOR (TW2003) AND RELATED CONSIDERATIONS**

**FACTORS POSSIBLY AFFECTING PROGNOSIS IN CHILDREN WITH WILMS’ TUMOR DIAGNOSED BEFORE 24 MONTHS OF AGE: A REPORT FROM THE ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA (AIEOP) WILMS TUMOR WORKING GROUP**

**REVIEW OF PHASE 1 AND II TRIALS FOR WILMS’ TUMOUR – CAN WE OPTIMISE THE SEARCH FOR NOVEL AGENTS?**
Brok J, Pritchard-Jones, Geller JI, Spreafico F
Eur J Cancer 2017; 79: 205-213

**HIGH DOSE TREATMENT FOR MALIGNANT Rhabdoid TUMOR OF THE KIDNEY: NO EVIDENCE FOR IMPROVED SURVIVAL – THE GESELLSCHAFT FÜR PÄDIATRISCHE ONKOLOGIE UND HÄMATOLOGIE (GPOH) EXPERIENCE**
Pediatr Blood Cancer 2017; 00:e26746. https://doi.org/10.1002/pbc.26746
IRINOTECAN FOR RELAPSED WILMS TUMOR IN PEDIATRIC PATIENTS: SIOP EXPERIENCE AND REVIEW OF THE LITERATURE; A REPORT FROM THE SIOP RENAL TUMOR STUDY GROUP (RTSG)

Ped Blood Cancer 2017; https://doi.org/10.1002/pbc.26849

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


2016

THE CLINICAL PHENOTYPE OF YWHAE-NUTM2B/E POSITIVE PEDIATRIC CLEAR CELL SARCOMA OF THE KIDNEY.

Genes Chromosomes Cancer 2016, 55: 143-147

GAIN OF 1Q AS A PROGNOSTIC BIOMARKER IN WILMS TUMOURS TREATED WITH PRE-OPTERATIVE CHEMOTHERAPY IN THE SIOP WT 2001 TRIAL: A SIOP RENAL TUMOURS BIOLOGY CONSORTIUM STUDY.

J Clin Oncol 2016; 34: 3195-3203

BIOLOGY AND TREATMENT OF RENAL TUMOURS OF CHILDHOOD.


IMPROVING CARE FOR CHILDREN WITH CANCER IN LOW- AND MIDDLE-INCOME COUNTRIES – A SIOP PODC INITIATIVE.

Arora RS, Challinor JM, Howard SC, Israels T.

IS NEPHRON SPARING SURGERY JUSTIFIED IN WILMS TUMOR WITH BECKWITH-WIEDEMANN SYNDROME OR ISOLATED HEMINEPHRECTOMY?


RIKS OF ADVERSE HEALT AND SOCIAL OUTCOMES UP TO 50 YEARS AFTER WILMS TUMOR: THE BRITISH CHILDHOOD CANCER SURVIVOR STUDY.

J Clin Oncol 2016; 34: 1772-1779


Irtan S, Erlrich PF, Pritchard-Jones K
Semin Pediatr Surg 2016;25:250-256

SIGNIFICANCE OF TP53 MUTATION IN WILMS TUMORS WITH DIFFUSE ANAPLASIA: A REPORT FROM THE CHILDREN’S ONCOLOGY GROUP

ASSOCIATION OF FOXM1 EXPRESSION WITH TUMOR HISTOLOGY AND PROGNOSIS IN WILMS TUMOR: POTENTIAL FOR A NEW PROGNOSTIC MARKER
Apelt N, Hubertus J, Mayr D, Graf N, Furtwangler R, Von Schweinitz D, Kappler R
Oncol Lett 2016; 12: 2854 – 2859

QUALITY-ASSURED CANCER SURGERY FOR WILMS TUMOUR: WHAT IS THE ROLE OF THE CLINICAL TRIAL GROUPS?
Powis M

WT1 MUTATION IN CHILDHOOD CANCER
Charlton J, Pritchard-Jones K
Methods Mol Biol 2016; 1467: 1-14

COMBINING miRNA AND mRNA EXPRESSION PROFILES IN WILMS TUMOR SUBTYPES
Int J Mol Sci 2016; 17: 475

EVIDENCE FOR A DELAY IN DIAGNOSIS OF WILMS' TUMOUR IN THE UK COMPARED WITH GERMANY: IMPLICATIONS FOR PRIMARY CARE FOR CHILDREN
Pritchard-Jones K, Graf N, van Tinteren H, Craft A
Arch Dis Child 2016; 101: 417-420

CHROMOSOMAL ANOMALIES AT 1q, 3, 16q, AND MUTATIONS OF SIX1 AND DROSHA GENES UNDERLIE WILMS TUMOR RECURRENCES
Oncotarget 2016; 7: 8908-8915

MULTI-OMICS ENRICHMENT ANALYSIS USING THE GENE TRAIL2 WEB SERVICE
Bioinformatics 2016; 32: 1502-1508

Our Website

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

It is a pleasure to inform you that the following paper has been awarded the SIOP 2017 Award for the best clinical abstract and presentation at the Congress in Washington, DC:

**MAPPING RELAPSE AND RELAPSE DETECTION OF WILMS’ TUMOR - A REPORT FROM THE SIOP RENAL TUMOR STUDY GROUP**

**Background and objective**
Children with Wilms tumor (WT) require regular relapse surveillance, usually with abdominal ultrasound and chest X-ray starting after surgery. We mapped the location, timing and mode of detection of first WT relapse using the SIOP WT 2001 trial database and assessed prognostic factors for post-relapse mortality. Data were used to evaluate current surveillance recommendations.

**Methods**
All patients with WTs registered (2001 - 2016) in the SIOP 2001 protocol and treated with pre-operative chemotherapy as per protocol were included in the analyses.

**Results**
Of 4348 registered patients, 538 (12%) relapsed. Relapse site predominantly involved lung (65%) and/or abdomen (49%), less frequently liver (11%), bone (1%) and central nervous system (1%). 5-year survival after relapse was 61% (95% CI: 57%-66%) and 75% of relapses occurred within 2 years post-surgery. Surveillance imaging captured 78% of the relapses and the remaining relapses presented with clinical symptoms ‘outside’ of routine follow-up. Relapse was identified by abdominal ultrasound (32%), chest X-ray (30%), CT scan of chest/abdomen (23%/7%), abdominal MRI (4%) or other (4%). The majority (69%) of relapses were not detectable by medical examination and only 33% of relapses were accompanied by symptoms. Multivariate analyses found significantly (P < 0.05) increased mortality risk after relapse for the following variables; surgery to relapse interval < 6 months, presentation with symptoms ‘outside’ planned follow-up, higher tumour volume at initial surgery, and advanced stage/histological risk group.

**Conclusion**
WT relapses predominantly involve the lung and generally occur within 2 years of nephrectomy and without symptoms. Current routine surveillance imaging captured the majority of relapses and these patients had better post-relapse survival. In the absence of prospective trials, the best available evidence indicates that current follow up recommendations are effective and should primarily be focused on the first two years after nephrectomy.
During the 49th Congress of the International Society of Paediatric Oncology (12-15 October 2017, Washington DC), Janna Hol was awarded the SIOP YI-NET Award for the abstract “Prognostic value of age in patients with Wilms tumour treated according to International Society of Paediatric Oncology (SIOP) 93-01 and SIOP 2001 protocols”, which she presented there.

Congratulations to Jesper and Janna and the co-authors, and we are looking forward to seeing the full papers published soon.
Further News

On the 30th of May 2017 Saskia Gooskens successfully defended her PhD thesis titled ‘Clear cell sarcoma of the kidney: clinical and molecular characteristics’ in Utrecht, The Netherlands (promotors: prof. dr. M.M. van den Heuvel-Eibrink and prof. dr. R. Pieters). The results of this thesis added knowledge to the existing clinical picture, started to unravel the molecular signature and provided potential targets for new treatments for CCSK in children. With this research project, Saskia won the Tom Voute award and SIOP Young Investigator award.

Congratulations to Saskia as well!
### Upcoming Meetings

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<tr>
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<td>5th to 7th of December, 2017</td>
<td>Atlanta, GA, United States</td>
<td>2nd Global Adolescent &amp; Young adult Cancer Congress</td>
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<tr>
<td>10th to 13th of April, 2018</td>
<td>St. Luis, MO, United States</td>
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<td>14th to 18th of April, 2018</td>
<td>Chicago, IL, United States</td>
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<td>1st to 5th of June 2018</td>
<td>Chicago, IL, United States</td>
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<td>11th and 12th of June, 2018</td>
<td>Copenhagen, Denmark</td>
<td>SIOP-RTSG Committee Meeting</td>
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<td>16th to 19th of November, 2018</td>
<td>Kyoto, Japan</td>
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### Impressum

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