

Newsletter



Renal Tumour
Study Group

Issue 1 January 2010

Contents

Editorial	1
SIOP-RTSG	2
Farewell party	4
Malaga Meeting	5
London Meeting	8
Statistical Report	10
Randomization	10
Biology	11
Relapsed Wilms	12
Publications	13
Impressions	15
News	16
Impressum	16

Editorial

Since 1971 SIOP (International Society of Paediatric Oncology) has conducted 6 prospective clinical trials (SIOP 1, SIOP 2, SIOP 5, SIOP 6, SIOP 9, SIOP 93-01) for children with nephroblastoma (Wilms Tumour). The seventh trial, SIOP WT 2001 is currently recruiting patients. The number of participating centres and countries has progressively increased. In December 2007 a new collaborative structure was proposed for the SIOP nephroblastoma group to take forward the planning and implementation of new studies in children and adolescents affected not only by Wilms Tumour, but by all kinds of kidney tumours. The group named itself SIOP-Renal Tumour Study Group (SIOP-RTSG).

As part of this approach we will publish an annual SIOP-RTSG Newsletter. This newsletter will introduce the groups involved in SIOP-RTSG, feature news and developments, highlight events, and provides updates on developments within and without SIOP-RTSG that are relevant to the Group's activities.

In this first issue, we focus on the agreed structure of SIOP RTSG and on the news from the last two meetings of the Group in Malaga, January 2009 and London, November 2009. We have now reached the point where sufficient patients have been recruited to the randomisation in the SIOP WT 2001 trial. The study remains open to patient registration for a further two years, however, the main reason being to find better biological markers for risk stratification. Find more in this newsletter. If you would like to know more about SIOP-RTSG, please visit our website (www.siop-rtsg.eu) or contact us (graf@uks.eu).

If you have any comments, ideas or suggestions based on this newsletter please let us know. We are open to additions and will be happy to receive articles from subcommittees for the next issue.

Norbert Graf

Kathy Pritchard-Jones

SIOP Renal Tumour Study Group (SIOP-RTSG)

SIOP-RTSG is initiated as a collaborative group within SIOP to focus on all aspects of kidney tumours in childhood, adolescents and young adults. In this respect SIOP-RTSG has an intergroup structure. It is acknowledged that the existing National Societies and Regional Groups participating in SIOP-RTSG will join their efforts and work closely together.

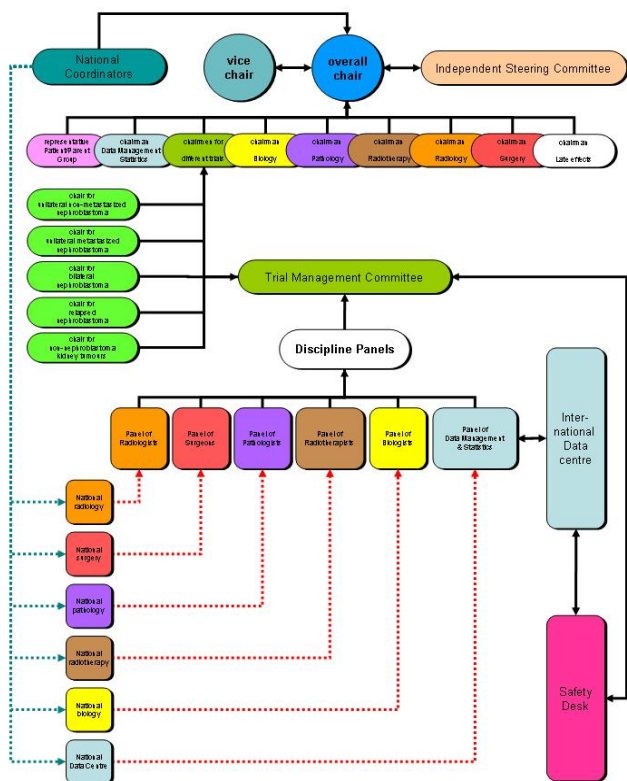
But they will also retain their existing structures in order to complete current studies and manage the contribution of centres in their own group towards new SIOP-RTSG trials and studies. There is exchange of information and cooperation with the COG in renal tumours. Members of the Board will participate in meetings of COG and vice versa. The building and running of common trials is desired and anticipated.

organisation of SIOP-RTSG and is supervising all activities within and outside of SIOP-RTSG dealing with renal tumours.

The Coordination Group of SIOP-RTSG includes representatives of all countries contributing to SIOP-RTSG trials and studies and the Chairs of the Discipline Panels. Defined groups of people will work on specific therapeutic areas. Five such areas have been defined so far (unilateral non-metastatic nephroblastoma, unilateral metastatic nephroblastoma, bilateral nephroblastoma, relapsed nephroblastoma, non-nephroblastoma renal Tumour).

Every effort will be undertaken to combine therapeutic questions into a minimum number of clinical trials to reduce bureaucracy as much as possible. Even though larger numbers of therapeutic areas are needed to be assessed for new therapeutic questions they can be addressed within few clinical trials. Panels will coordinate the contribution of their members to provide expert advice and evaluation of specific aspects of trial data or protocol requirements. SIOP-RTSG trials and studies recruit patients across a wide range of countries each of which have their own structures, languages and legal requirements.

The role of the National Coordinator (NC) is critically important to the successful conduct of a study in each participating country / regional group. The NC will liaise with the SIOP-RTSG to address the problems in the implementation of the study in his/her own country / group. All countries participating in SIOP-RTSG trials and studies must be represented by a NC. The most important task of SIOP-RTSG is to get better treatment with higher



SIOP-RTSG has a Board, a Coordination Group, National Coordinators, Discipline Panels, and other committees. The composition of the different subgroups as well as their composition, duties and responsibilities are given in table 1.

Members of the SIOP-RTSG Board are the chair (Norbert Graf) and vice chair (Kathy Pritchard-Jones) and the national coordinators. The board has to plan the strategic direction and the

Up to now the following panels have been identified	
Radiology	(chair: NN)
Surgery	(chair: Jan Godzinsky)
Pathology	(chair: Bengt Sandstedt)
Radiotherapy	(chair: Foppe Oldenburger)
Biology	(chair: Kathy Pritchard-Jones)
Safety Desk	(chair: Christophe Bergeron)
Late effects	(chair: Gill Levitt)
Data management & Statistics	(chair: Harm van Tinteren)
Parents Group	(chair: NN)



Denomination	Acronym	Composition	Notes
SIOP-RTSG Board	Board	<ul style="list-style-type: none"> • SIOP-RTSG Chair and Vice Chair • National coordinators 	Planning the strategic direction, organisation, supervision
SIOP-RTSG Coordination Group	CG	<ul style="list-style-type: none"> • Board members • Chairman of different panels • Representative of Patient/Parent Group • Trial Management Committee • International Data Centre • SIOP-RTSG Safety Desk 	Collaborate with the TMC, review the progress of trials, approve protocol modifications
National Coordinators	NC	Representative of each country participating in SIOP-RTSG trials and studies	Promote SIOP-RTSG in their own country, responsible for regulatory, ethical and financial issues, and data management in their own country
Discipline Panels	DP	Groups of experts in the different disciplines supporting SIOP-RTSG trials and studies	Provide expert advice
Trial Management Committee	TMC	<ul style="list-style-type: none"> • CG Investigators • NC Representatives • DP Representatives 	Monitor and supervise trials Advice on publicity and presentation of the trials
Data Management & Statistical Committee	DMSC	<ul style="list-style-type: none"> • Principal biostatistician • National biostatisticians • Chief investigators 	Provide a RDE system, prepare the reports for meetings
International Data Centre	IDC	Head of the IDC and IDC staff	Provide annual progress report and annual safety report
Independent Steering Committee	ISC	Independent experts in the field of oncology	Recommend and supervise non-randomized trials and studies regarding pharmacovigilance, addressing relevant questions
Independent Data Monitoring Committee	IDMC	Independent experts in the field of kidney tumours	Review patient accrual and involvement according to the statistical plan within trials, recommendations to the TMC e.g. on toxicity and safety issues
SIOP-RTSG Safety Desk	SD	Two clinicians designated by the board to have oversight of safety monitoring and pharmacovigilance procedures	Responsible for the evaluation and response to all SAEs and SUSARs
Representative of Patient/Parent Group	RPG	One to two representatives from parents	Give input about burning questions from patient's view, review informed consents, engage in fundraising

cure rates, less acute toxicities and late effects for the sake of children and young adults with kidney tumours. This goal can only be achieved by enrolling as many patients as possible in prospective clinico-genomic trials and by fostering basic research.

Clinico-genomic trials facilitate the analysis of combined datasets from molecular biology and clinical trials. This will help to find new risk factors, better treatments and at the end higher cure rates. New Countries or new centres who wish to participate in SIOP-RTSG can apply for membership at any time by contacting the chairman. They have to demonstrate their ability to meet all requirements of the group.

More information about SIOP-RTSG can be found on our website (www.siop-rtsg.eu). For members of SIOP-RTSG the 'Structures and Standards for SIOP-RTSG' document can be downloaded from the Intranet.

Farewell Party for Jan de Kraker

On the 9th of September 2009, the farewell symposium of Dr. Jan de Kraker took place in Amsterdam.

Jan started his career as one of the pioneers in the field of paediatric oncology and contributed to the development of treatment of paediatric cancer with great authenticity. He has been mainly involved in the development of national and international treatment protocols for solid tumours, mainly hepatoblastoma, neuroblastoma and nephroblastoma.

Over the last decades as international chair of SIOP Wilms tumour protocols, he managed to involve most European countries and even Brazil. In addition, in the last decades his efforts extended to outreach projects in Morocco and Malawi in order to improve outcome of children with renal tumours in less favourable circumstances.

He has been an inspiring teacher for many younger colleagues over the years. His modesty and open mind for new ideas have been very important determinants of the successful management of the mentioned treatment projects involving so many different colleagues and groups.

The farewell symposium was a true reflection of all his activities and passions, and the after-party underscored this by going back to his youth in Surinam, enlighten by Antillean music and dance, being surrounded by his close family, friends, and Dutch as well as international colleagues.

SIOP-RTSG is thankful for his outstanding contributions to Wilms Tumour in all aspects. We are happy that he will continue to work with us. His advice will guide us to develop better treatments for children with nephroblastoma in the future.

Marry van den Heuvel-Eibrink
Rotterdam, The Netherlands



Impressions to be continued on page 15

SIOP-RTSG Meeting in Malaga, 16th–17th January, 2009

The first SIOP-RTSG meeting this year was held in Malaga. Tomás Acha and his team hosted the two day meeting of the RTSG group.

On the first day issues concerning the SIOP 2001 study were discussed. A new interim report provided by Harm van Tinteren and the Amsterdam Team was discussed. Up to now there is no reason to stop the trial. The randomized question will need patient entry at least to the end of 2009. The committee expressed a preference for trying to keep the current study open even after closure of the randomized arm, with a coordinated effort to get more biological samples collected and to analyze putative biomarkers on a large sample size of paraffin tissue from the current patients enrolled to date. If this can be done for the next 2-3 years sufficient numbers will be obtained to address some of the biological questions with better power for a next trial. An amendment to the current study will be provided at that time when the randomization will stop.

Reports of the different panels (surgery, pathology, radiology, radiotherapy and biology) were given by the chairmen and lively discussed. During the surgical session renal sparing surgery in unilateral cases was the main topic. It was agreed that such surgeries should be done centralized and reviewed by the surgical panel upfront to advice local centres. A plea of pathologists is to increase the number of slides send by local pathologists for reviewing. This number has to be increased in different countries. Pathological diagnosis is depending on a good quality and numbers (at least 10 slides) of slides.



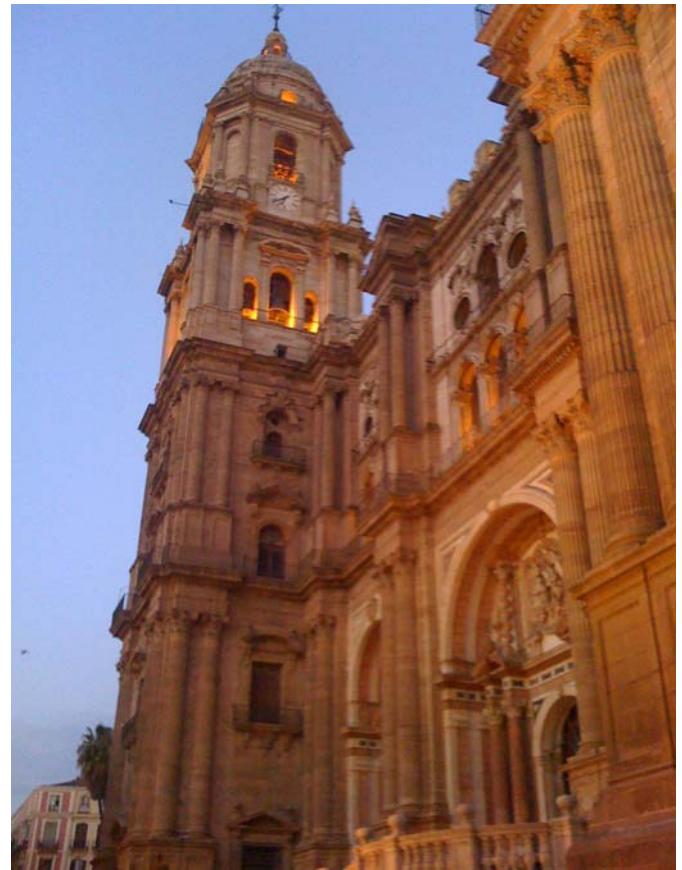
The classification of nephroblastoma is often not easy for local pathologists because of the rarity of the tumour. There is still a 15 % discrepancy between local and reference pathology. A new and easier classification will be discussed for the next trial taking only the amount of blastema and necrosis as the most relevant features into consideration. In addition educational material will be provided by the pathologists and put on the SIOP-RTSG webpage. It is a great success that the panel of radiologists is getting more actively engaged in the Wilms Tumour trials. For the next trial a prospective centralised review is anticipated. The technical details have to be elaborated to send the imaging files directly from local hospitals from their PACS system to the central reviewer. Standardized criteria for imaging studies in renal tumours in children will be developed for the next trial. This will be accompanied by prospective radiological questions as well as a standard follow-up schema during and after treatment. Regarding radiotherapy there might be a group of children with stage III intermediate risk, who do not need irradiation. Up to now such a group cannot be defined. Molecular markers may distinguish between patients who do need and those who do not need radiotherapy. After a short overview about recent developments and findings in WT-gene research (3% WT patients with constitutional epigenetic changes at the H19 DMR (11p15.5) locus, WT-X gene (Dan Haber), expression of MYCN: gain adversely correlates with outcome), KPJ summarized the ongoing molecular research on CCLG/SIOP Wilms-Tumors.

On the second day Tomás Acha presented the structure of the Wilms Tumour Group in Spain. A great effort was done during the last few years. This is explicitly honoured by SIOP-RTSG. At the moment the Spanish group is focusing on increasing recruitment and pathological review as well as retrieving missing data. Biobanking has already started. There are already frozen samples from about 85 tumours available.

A long and intensive discussion followed addressing the next prospective trial. Key question will be asked in localized and in metastatic Wilms Tumour. Molecular markers are awaited for stratification. The logistics of the prospective trial(s) have to be improved to fulfil the requirements of the EU regulations concerning clinical trials. Most important is a common data management system with RDE features and integration of an imaging module for reference radiology. Biobanking and tissue exchange has to be enhanced. An important issue will be overhead structure funding in future. On a national level every country has to apply for its own funding.

The first trial that will start after SIOP-RTSG was established will be the relapsed study. Filippo Spreafico is doing a great job in organizing this trial. After a long period of time trying to run a transatlantic study randomizing high-dose chemotherapy with stem cell rescue and conventional chemotherapy it is now clear it is very difficult for resources to be priori. To improve the knowledge about the most recent treatment concepts and results in the participating groups Filippo Spreafico will retrospectively analyse the patterns of relapse and especially the role of Topotecan for all relapses between 2000 and 2008. Treatment recommendations will be finalised based on this analysis with the option to join the relapse study of COG for high risk relapses. SIOP-RTSG will provide a protocol for all patients with a nephroblastoma relapse taking different risk groups into consideration. Paul Grundy explained the AREN0921 study of ICE-T for children with high risk recurrent favourable histology Wilms Tumour. COG will accept patients from SIOP. One central data centre for SIOP-RTSG using the COG-RDE system is possible and can be in Milan. Such a cooperation with COG can be a test case for further collaborative trials and is therefore more than welcome.

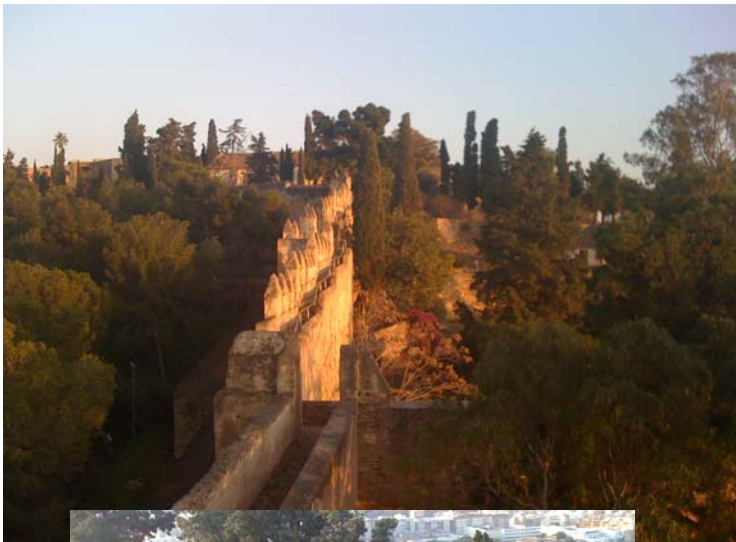
The whole meeting was a great success not only from a scientific point of view but also because of the hospitality and the more than friendly atmosphere.



A visit of the Picasso Museum in Malaga and a great Dinner made the whole meeting just perfect. A visit at the end of the meeting to the Castle of Alcazaba, which reigns over the city, assured all of us to come back.

For minutes of the Malaga meeting please refer to the RTSG Documents section on our webpage (www.siop-rtsg.eu).





SIOP-RTSG Meeting in London, 25th–26th November, 2009

The second SIOP-RTSG meeting this year was held in London. Kathy Pritchard-Jones and her team hosted the two day meeting of the RTSG group. On the first day issues concerning the SIOP 2001 study were discussed. A new interim report provided by Harm van Tinteren and the Amsterdam Team was discussed. The randomised question will be stopped at the end of 2009. A letter informing all participating centres is on the way. The committee explained that the current study will continue for 2 more years up to the end of 2011. After the end of the randomisation patients with localized unilateral disease with intermediate risk and stage II or III will receive the standard treatment with three drugs (AVD). During the upcoming 2 years a coordinated effort will be done to get more biological samples collected and to analyse putative biomarkers on a large sample size. This will help to address some of the biological questions with better power for the next trial.

Much time was spent regarding the next trial and study and addressed separately for unilateral tumours, bilateral tumours, metastatic tumours, Non-Wilms tumours and relapsed tumours. Up to now no trial question(s) is (are) defined. Further analysis to find better biological risk factors have to be undertaken. It was agreed that for the next trial an IT-infrastructure with a central database, a DICOM server and RDE (remote data entry) features has to be implemented. The infrastructure of ACGT (Advancing clinicogenomic trials for cancer; an integrated project of the 6th framework package of the EU) might be a possibility. This will be further investigated. Data for the different treatment groups have to be collected prospectively including side effects (Kidney function, heart function, etc.) with the help of simpler forms (CRFs). Each treatment group will elaborate drafts of possible treatment protocols for the next meeting. In case of bilateral tumours a discussion should be undertaken with the COG to collect similar data for comparing the different approaches of preoperative chemotherapy. In COG three drugs (AVD) will be used from the beginning whereas only two drugs (AV) will be used in SIOP. In relapsed tumours SIOP decided to join the COG trial for high risk relapsed patients (AREN1021). In case of rare kidney tumours (RCC and CCSK) a close cooperation between COG and SIOP is appreciated. Elizabeth Mullen presented data from COG regarding their approach in Wilms' Tumour. The objectives of the trials were outlined and discussed. In COG LOH of 1p and 16q is used for

stratification of patients. The good cooperation between COG and SIOP was emphasized.

Trijn Israels and M'hamed Harif presented data on treatment of patients with Wilms' Tumour in Africa. The initiative to treat patients in Malawi is highly appreciated by SIOP-RTSG. At presentation these children have large tumours and many suffer from metastatic disease. One of the biggest problems is abandonment and malnutrition. Unfortunately radiotherapy isn't available in Sub-Saharan Africa. Support from SIOP-RTSG will be given for this outstanding work in Africa in future.

Reports of the different panels (surgery, pathology, radiology, radiotherapy and biology) were given by the chairmen and lively discussed during the second day. Pathologists have to meet with the statisticians to further explore the amount of blastema as the major risk factor in histology besides anaplasia and stage. A big concern is the difference in local stage distribution between the different countries. For an upcoming trial clear definitions have to be defined precisely. Again pathological diagnosis is depending on a good quality and numbers of slides (at least 10 slides).

During the surgical session nephron sparing surgery in unilateral cases, minimal invasive surgery and sentinel lymph node detection were the most important topics. It was agreed that such surgeries should be done centralized and reviewed by the surgical panel upfront to advise local centres. It has to be mentioned that for the first time the panel of surgeons did meet separately on the first day.

It is a great success that the panel of radiologists is now actively enrolled in the Wilms Tumour trials. Their presentations were highly appreciated. For the next trial a prospective centralised review will take place. The technical details have to be elaborated to send the imaging files directly from local hospitals from their PACS system to the central reviewer. Standardized criteria for imaging studies in renal tumours in children will be developed for the next trial. This will be accompanied by prospective radiological questions as well as a standard follow-up schema during and after Treatment.

Regarding radiotherapy data will be analyzed to give new recommendations for stage III patients with completely necrotic lymph nodes. It is important to

enrol more Radiotherapists in SIOP-RTSG. After an overview about recent developments and findings in WT-gene research interesting data were shown on Retinoic acid (RA) and Wilms' tumour. Further analysis of the retinoic acid pathway in nephroblastoma and in vitro assays will be done to find the real impact of retinoic acid in nephroblastomatosis. In cases of progressive disease RA might be given as compassionate use. During this session the need for more snap frozen tumour material was stressed.

Kathy Pritchard-Jones did present the European Network of Cancer research for children and adolescents (ENCCA). SIOP and other major stakeholders in the field of Paediatric Oncology in Europe have worked together to apply for a grant of the 7th framework package of the EU. SIOP-RTSG is part of this Network of Excellence (NoE). WP 2.4.3 deals with the implementation of a prospective WT clinical study in the ACGT system. (ACGT: Advancing clinicogenomic Trials in Cancer, an integrated project funded in FP6 of the EU: www.eu-acgt.org).



How to proceed with rare kidney tumours was discussed mainly for rhabdoid tumours (RTK) and Renal Cell Carcinoma (RCC). In RTK a European registry is established and ready for registration of such patients. A protocol of the registry will be provided via the SIOP-RTSG webpage as soon as the protocol has passed ethical approval. RCC is responsible for 2-6% of all paediatric renal tumours. There is a difference in biology of RCC between children and adults which is discussed further. Prognosis for localized disease is excellent after surgery alone. In case of metastasis beyond regional lymphnodes new treatment options are needed. Targeted therapies are discussed. In case of lymph node involvement radical dissection of these nodes is recommended in childhood and young adults.

Norbert Graf presented improvements on the SIOP-RTSG Homepage. He emphasized the advantages of the intranet options where members can find the mailing list, minutes, amendments, meetings, interim reports, forms, management board, etc.. Different panels and treatment groups are asked to hand in short & comprehensive documents about their activities for the public presentation section. There is also the need for information about Wilms' Tumour for the public and for specialists as training material.

The whole meeting was again a great success not only from a scientific point of view but also because of the hospitality and the more than friendly atmosphere and not only during a great Dinner at the evening of the first day. SIOP RTSG are grateful to Pfizer Ltd for support for this meeting.



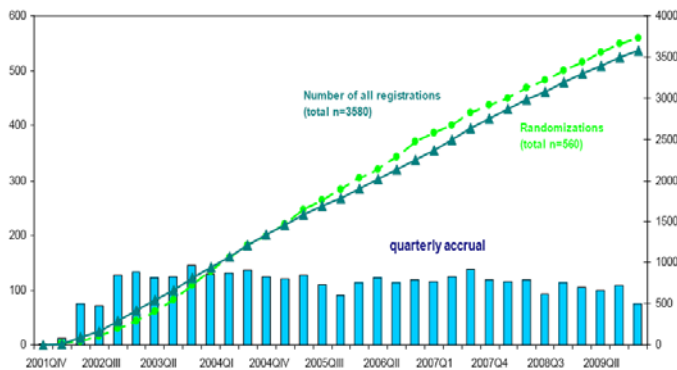
Our next meeting will be held on the 17th & 18th of May 2010 in Homburg / Germany

Latest interim statistical report

The Nephroblastoma study and trial protocol 2001 started accrual in June 2001. The data presented in the 9th interim report refers to the data that have been received and processed continuously by the regional centres until November, 2009. A total of 3583 patients have been included in the database of which 560 children are randomized.

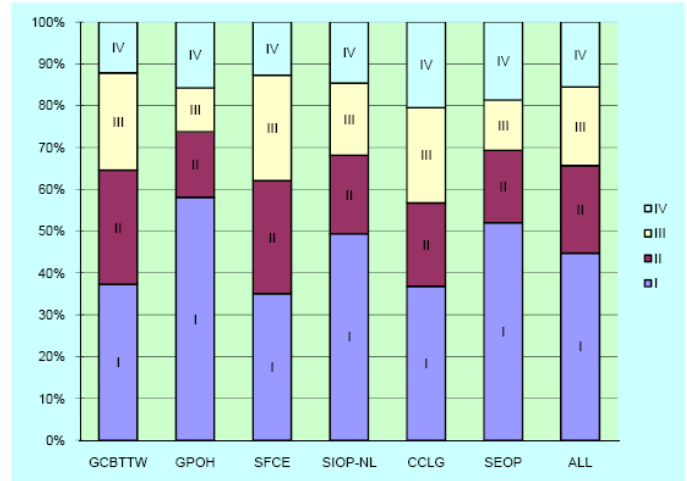
The yearly number of registrations is quite constant as given in the following figure also showing the cumulative total number of all patients and of the randomized patients. The average quarterly accrual is about 120 patients in total and every three months 15-20 patients are randomised (figure 1).

Figure 1: Quarterly accrual - All Patients



One of the most striking and unexplained findings is the difference in stage distribution between different national groups (figure 2). Further investigations are necessary to draw conclusions.

Figure 2: Stage localized and metastatic Wilms' tumours



You can download the *Interim statistical report 2009* in the RTSG documents section of our webpage (<http://siop-rtsg.eu>).

Closure of randomization

On 20th May 2009, the Independent Data Monitoring Committee (IDMC) discussed the proceedings of the SIOP WT 2001 randomised controlled trial of adjuvant chemotherapy with or without Doxorubicin in patients with stage II or stage III intermediate risk nephroblastoma. The discussion was based on the fourth interim report that was prepared by the Trial Secretariat and disseminated to the IDMC on April 24th, 2009. At this time, the advice of the IDMC was to continue randomisation until at least 550 eligible patients had been randomized. This target was predicted to be reached by the end of 2009.

The advice of the IDMC was discussed within the Trial Steering committee and with all members of the SIOP Renal Tumour Study Group (RSTG) during the Committee meeting of the 22nd-23rd November 2009 in London. As 581 patients have now been randomized, the Steering committee agreed that the randomisation should close with effect for any patient registered after 1st December 2009 (since

they would not be eligible for randomisation until after week 4 of treatment, i.e. after 31st December 2009). Following closure of the randomisation, the recommended post-operative chemotherapy for patients with stage II/III intermediate risk histology Wilms tumour reverts to the standard three drug arm of the current trial (i.e. vincristine, actinomycin D and doxorubicin according to schedule AVD). This recommendation will remain in force until it can be reviewed in the light of the first analysis of the trial. The IDMC have advised that the preliminary results of the randomisation can be made available to the trial steering committee once the last randomised patient has finished treatment, i.e. after July 2010. The protocol states that the final analysis of the primary efficacy endpoint (EFS) will only be performed when there is a minimum of 2 years follow up on the final randomised patient. The IDMC strongly recommends to follow up all patients for a long time (at least 7-10 years) to obtain information on the results of salvage treatment on recurrences, the long term potential adverse effects of doxo-

rubicin on cardiotoxicity and survival. The IDMC also emphasises that the primary responsibility for patient treatment lies with the treating physician. The IDMC also states that the final responsibility for treating patients is with the treating physician.

The SIOP WT clinical trial and study will remain open to patient registration for a further 2 years following closure of the randomised arm, i.e. until

Dec 31st 2011. This is to ensure sufficient patient accrual to allow adequately powered conclusions to be drawn from the single arm treatment recommendations for the new high risk blastemal type subgroup and the response-adapted approaches to treatment of metastatic and bilateral tumours. A major focus of the trial will therefore be to ensure storage of an adequate amount of frozen tumour and adjacent normal kidney from as many patients as possible in the coming two years.

Biology of Wilms Tumour

Existing prognostic factors in Wilms tumour identify only half of the children who subsequently relapse. The SIOP WT 2001 trial uses *in vivo* histological response to pre-nephrectomy chemotherapy to define a new high risk 'blastemal' subtype. The molecular marker of loss of heterozygosity (LOH) at 1p36/16q21-24 is now used in chemotherapy naïve tumours in COG trials. Both groups classify tumours with diffuse anaplasia as high risk. However, neither group's approach is sufficiently sensitive or specific to identify the majority of patients with poor outcome: 'high risk' histology (blastemal type or diffuse anaplasia) is found in only ~25% of all relapses with the SIOP approach, and combined LOH 1p/16q occurs in only ~10% of all relapses with the COG approach. The interrelationship of the two risk classification schemes is not yet established though our preliminary analyses show that LOH 1p and/or 16q is found across all of the SIOP histological risk groups. It is likely that multiple prognostic factors will be required to accurately define the highest risk group. Conversely, there is a need to more reliably identify patients whose current treatment can be safely reduced, e.g. by omission of doxorubicin.

Hence, an important aim of the SIOP WT 2001 trial and study is assemble a sufficiently large and representative high quality sample set that will permit comprehensive biological studies. The number of samples analysed must provide robust assessment of a variety of molecular markers suggested from retrospective studies and establish their relationship with clinical outcome and histological risk group (see table). An important aim is to define the molecular characteristics of 'resistant' blastema, and hopefully simplify the current, somewhat subjective, approach to defining blastemal type Wilms tumour on morphological grounds. The ultimate aim is to develop an algorithm that combines molecular features and histological response to improve risk stratification and to better define the characteristics of the higher risk subgroups to define targets for new therapeutic approaches.

*Sample size calculations are based on the ability to analyse prognostic impact within the uniformly treated stage I group. This can be augmented by stage II tumours that will have been randomised to similar treatment with only vincristine and actinomycin D.

Markers to be analysed in the initial phase include LOH 1p/16q, gain of 1q21-25 (found in ~30% of tumours), alterations in copy number of *MYCN* (present in ~5% of tumours and apparently associated with diffuse anaplasia), alterations in some *MYCN* regulatory factors and copy number/mutation in the known WT genes (*WT1*, *WTX*).

Samples required

Analysis of LOH 1p and 16q can be performed on formalin-fixed, paraffin embedded tissues but requires matching normal tissue (adjacent kidney or blood). Paired samples from ~1,500 patients need to be analysed, of which ~50% should be stage I (i.e. 750) with up to a further 150 stage II treated with only AV-2 chemotherapy. The success of this analysis requires samples to be made available from at least half the patients enrolled in the study.

In parallel, an MLPA-based assay is being developed to simultaneously assess copy number at a variety of loci of interest. This technique requires access to frozen tumour tissue but does not need matching normal tissue. MLPA will be performed on up to ~800 tumours to allow for an expected higher failure rate due to more stringent DNA quality requirements. It will allow assessment of LOH 1p/16q as this is mainly due to genomic loss rather than copy neutral changes. Collection of these samples for biological studies will also underpin further biomarker studies in Wilms and other renal tumours, for which there is an unmet clinical need.

Access to samples for additional biological studies

All samples submitted for the above centralised biological studies remain under the control of the submitting national group. Application for use of SIOP WT samples to explore further hypotheses is by application to the SIOP WT Biology Committee .

Table: Sample size calculations*

Biomarker	Prevalence	Impact on 2yr relapse free survival	Estimated no. of patients	No. of events	Hazard ratio
1p LOH	11%	90->80%	809	100	2.12
16q LOH	15%	90->75%	301	42	2.73
Combined	5%	90->75%	787	94	2.73
1p/16 LOH					
1q gain	30%	90->75%	191	31	2.73
MYCN gain	5%	90->50%	136	18	6.58
MYCN gain	5%	90->30%	64	9	11.43

2-sided alpha = 0.05, power 80 %

Kathy Pritchard-Jones, London, UK

Strategy for relapsed Wilms Tumour

The evidence for the optimal retrieval therapy for recurrent Wilms tumour (WT) comes from limited experiences. Overall, chemotherapy regimens testing the efficacy of ifosfamide, cyclophosphamide, etoposide, and carboplatin have been used. However, the lack of homogeneity among the reported cohorts of patients makes it difficult to compare these agents, their combination and dose-intensity, above all concerning the role of high-dose chemotherapy and autologous hemopoietic stem cell rescue (ASCR). The EBMT registry shows us a diffuse attitude to use ASCR in recurrent WTs, however often outside controlled clinical trials. Although an international cooperative group randomised trial was mooted to address this question, it has not been possible to take this forward at the present time due to the long time frame for recruitment.

Implementing clinical trials for relapsed WT patients in Europe remains challenging. Such trials require multinational participation to achieve adequate power. The achievement of a coordinated study would be preferable, not only in terms of the more precise clinical questions that could be addressed, but through the opportunity to conduct translational research into the biological basis of recurrent WT on a larger scale. There are only scanty data on the specific cellular pathways involved in tumour progression or metastasis, mainly relating to presence of TP53 mutations. There is a clinical need to define the involvement of pathways for which targeted therapies already exist in the progression or relapse of WT.

During the Malaga and London meetings, the basis of possible future projects on relapse, including cooperation with COG, have been laid. The general consensus on the starting points to develop a shared strategy for treatment of recurrent WT patients and onto which additional clinical and biological questions can be added, are:

1. *standard-risk* recurrent patients (initial stage I or II initially treated with two drugs only, non anaplastic histology): treatment approach to this group is less standardized, owing to the small number of such patients, with the adoption of different regimens between countries, almost always including doxorubicin, etoposide and an alkylating agent. SIOP-RTSG will work on sharing homogeneous therapy recommendations, with the aim of maintaining satisfactory DFS (~70%);

2. *high-risk*: the most significant factor associated with a worst post-relapse outcome in favourable-histology WTs (i.e. non anaplastic, and not blastemal type after chemotherapy) seems to be the previous use of doxorubicin. This group displayed a DFS ranging between 40-60%, mostly with the use of intense-dose chemotherapy or high-dose chemotherapy with ASCR. The ifosfamide-carboplatin-etoposide combination emerged as probably the most effective retrieval treatment. Evidence on how to properly administer surgery and radiotherapy is more fragmentary. SIOP-RTSG will promote a strict cooperation with COG, which is finalizing a phase II study aimed to test the feasibility of adding topotecan to ICE chemotherapy (AREN1021);
3. *very-high-risk*: this group might include those with diffuse anaplasia, regardless of pre-treatment or not, or blastemal-type after preoperative chemotherapy. For these children, who have likely developed chemoresistant tumours, inclusion in trials of novel agents is warranted. We believe it is important to participate in the discussion of other groups specifically interested in developing new drugs/strategies, like ITCC. Indeed, ITCC is planning to host meetings with each of the tumour specific trial groups to assist with formulation of a relevant drug development strategy for each tumour type. This will be facilitated as part of the ENCCA FP7 project.

Together with these prospective activities, a more comprehensive retrospective analysis on a larger number of recurrent patients, and focusing on critical burning questions (why recurrence in low-stage low-risk tumours? Why recurrence after many years since diagnosis?) might help us to improve the development of first-line strategies for WT as well.

In conclusion, any further reductions of intensity of first-line therapy must incorporate standardised treatment recommendations for patients whose tumours recur in relation to the intensity of their first line therapy. A small increased risk of relapse after reduced therapy for good risk patients would only be acceptable if the salvage therapy was likely to be very successful and tolerable in the short and long term.

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Impressions





News and upcoming events

2 nd -3 rd March 2010	Banff, Canada	7 th International Conference on the Biology of Childhood Renal Tumours
17 th -18 th May 2010	Homburg, Germany	SIOP-RTSG Committee Meeting

Please save the date! March 1-3, 2010



Photo by Teana Imbeau

Please save the date!

The 7th International Meeting on the Biology of Childhood Renal Tumors will be held on March 1-3, 2010 at the Rimrock Resort Hotel in Banff, Alberta, Canada.

This meeting follows on from the previous successful meetings, to bring together scientists and clinicians with an interest in understanding the biological basis of childhood renal tumors and how this can be translated into improved approaches to treatment.

This year the meeting will take place over three full days (March 1, 2 and 3, 2010) in Banff, Alberta, Canada.

This will be an exciting conference with the opportunity to ski following. Please bring this to the attention of anyone who might be interested.

Paul Grundy
Kathy Pritchard-Jones
Jeff Dome
Norbert Graf

<http://bcrtconference.com>

Impressum

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