Editorial

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

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*Dedicated to Jan de Kraker, chair of SIOP RTSG from 1993-2008

Nephroblastoma or Wilms tumor (WT) was one of the first childhood cancers shown to be curable with ~10-15% survival even when treated with surgery alone and it was also the first solid tumor where lung metastases were successfully treated with the addition of actinomycin and radiotherapy in early 1960s. Shortly after, two study groups - the International Society of Paediatric Oncology (SIOP) in Europe, and the National Wilms Tumor Study group (NWTSG) in Northern America – were formed and started running prospective and randomized trials intended to find optimal treatment for children with WT. At the initial SIOP meetings held in Madrid (1969), Lyon (1970) and Mainz (1971), the "purpose, scope and outline of a prospective SIOP trial for WT was discussed and approved",[1] and in 1971 the first patient was enrolled in the SIOP-1 study. Since then, seven clinical studies and randomized trials have been completed by SIOP (Fig 1). SIOP focused on the relative merits of pre-nephrectomy treatment in contrast to NWTSG pursuing immediate surgery. The recently started SIOP-RTSG 2016 UMBRELLA study is recruiting patients from the most of Europe and from the other continents.

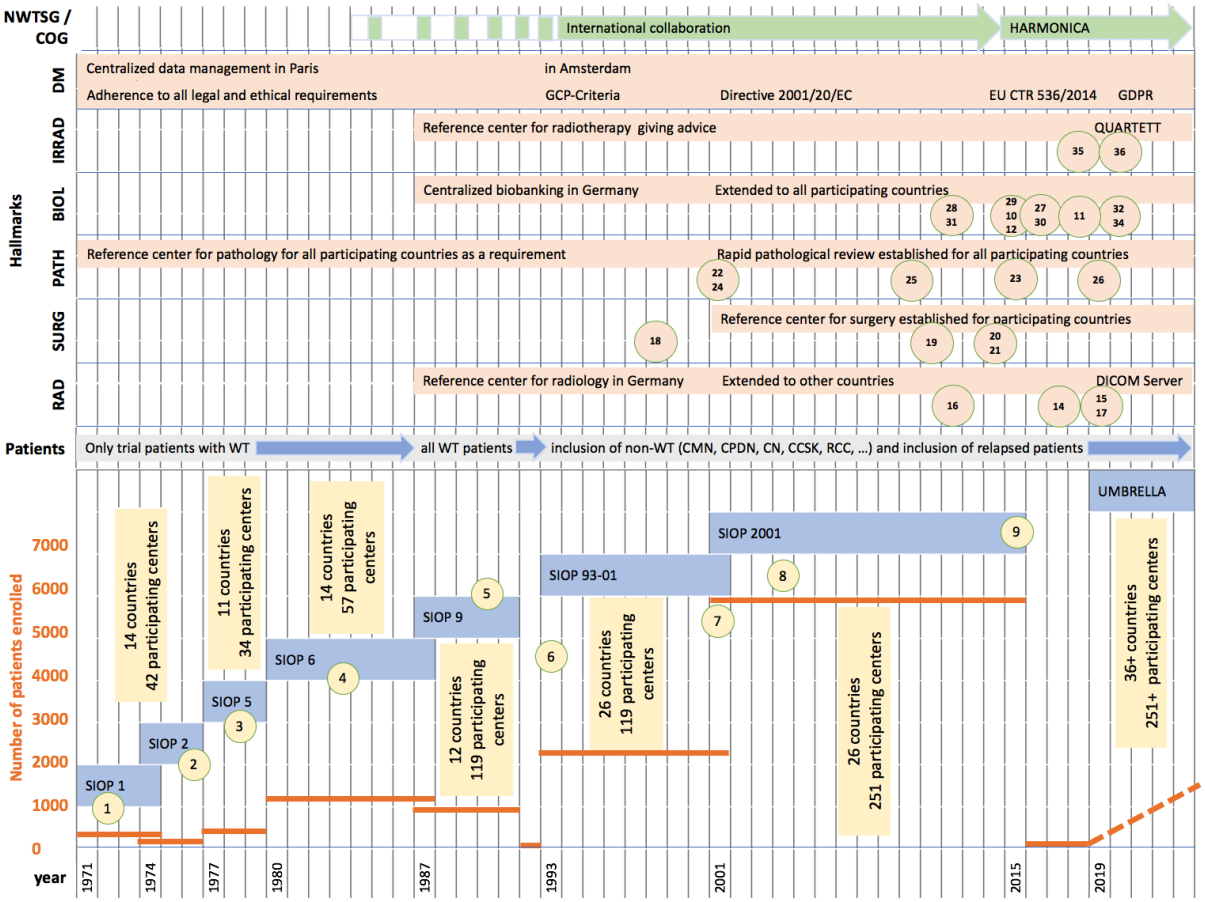

Figure 1: Clinical trials for childhood renal tumors over time. Numbers in circles refer to the corresponding references; GCP: Good Clinical Practice; 2001/20/EC: Clinical Trial Directive; CTR: Clinical Trial Regulation; GDPR: General Data Protection Regulation; QUARTETT: Platform for Radiotherapy Consultation; WT: Wilms tumor; MN: congenital mesoblastic nephroma; CPDN: cystic partially differentiated nephroblastoma; CN: cystic nephroma; CCSK: clear cell sarcoma of the kidney; RCC: renal cell carcinoma

In the first three trials (SIOP 1, 2 and 5) the benefits of pre-operative treatment in WT were established. This approach resulted in safer operations with fewer tumor ruptures, and a favorable postoperative stage distribution allowing less treatment after surgery. [2-4] The fourth

trial (SIOP 6) was the first to introduce stratification according to stage and histology, determining a risk-adapted post-surgical treatment.[5] Duration and intensity of chemotherapy was randomized in local stages building the basis for future trials, and less than 1/3 of patients need to receive radiotherapy since. In parallel, a pilot study was completed for patients with metastatic tumors, showing that a 3-drug pre-operative chemotherapy regimen (vincristine, actinomycin and doxorubicin [AVD]) is efficient and allows omission of lung irradiation in >70% of patients in complete remission after pre-operative chemotherapy and surgery.[6] It was concluded that stratification of treatment according to risk factors could significantly limit acute and late toxicity and lead to ~90% overall survival after 5 years for the entire group of WT patients.[5] Four weeks of pre-operative chemotherapy in localized WT with vincristine and actinomycin (AV) was found to be the gold standard in SIOP-9.[7] After SIOP 93-01 trial, postoperative chemotherapy in localized stage I intermediate risk WT (IR-WT) was reduced from 18 to 4 weeks of AV.[8] As IR-WTs stage I account for >50% of localized WTs, a majority of WTs is now cured with only 8 weeks of 2-drug AV chemotherapy (4 weeks pre- and 4 weeks post-operatively) and nephrectomy. Besides living with a solitary kidney after surgery, other long-term sequelae are negligible in most WT survivors receiving this minimal treatment. To further reduce late toxicities without compromising the high survival rates, in SIOP 2001 trial the use of anthracyclines was randomized in localized stage II and III IR-WTs. Overall survival rates were superimposable (~95%) for patients who were treated with and without doxorubicin.[9] Parallel molecular studies have identified numerous driver genes in WT and non-WTs, some being candidates for prognostic biomarkers or therapeutic leads.[10-12]

The current UMBRELLA study aims to facilitate the best possible diagnostics and treatment for all children and adolescents with renal tumors. By collecting and analysing biomaterial systematically, the goal is to find new biomarkers and better stratification parameters for future trials.[13] Furthermore, for the subgroup of stage IV WT patients a randomized trial will explore whether a less toxic pre-operative chemotherapy with carboplatin, etoposide and vincristine is as effective as AVD. Another trial is prepared asking the question whether highly conformal radiotherapy is as effective as conventional regimens.

Since SIOP 93-01 trial patients with non-WTs are registered, and since UMBRELLA study specific guidelines are provided including diagnostic and treatment recommendations. In addition, guidelines for adult WT are given.

Although renal tumors in childhood are rare, >10,000 patients from over 260 centers across 36 countries have been enrolled and treated according to SIOP protocols (Fig. 1). As the number of centers participating in SIOP WT trials is increasing, the SIOP Renal Tumour Study Group (RTSG) Association was founded in 2021 (Fig. 2) to deal better with our main mission of increasing survival rates and reducing acute treatment toxicity and late effects in patients with renal tumors. SIOP-RTSG aims to offer the same standardized high-quality diagnostics and treatment to all patients, irrespectively of the tumor type, their socio-economic status or the geographic region where patients live. In this respect kidney cancer in childhood will serve as a paradigm for rare cancers, which is in line with the aspirations of both SIOP, and the WHO global initiative in childhood cancer.

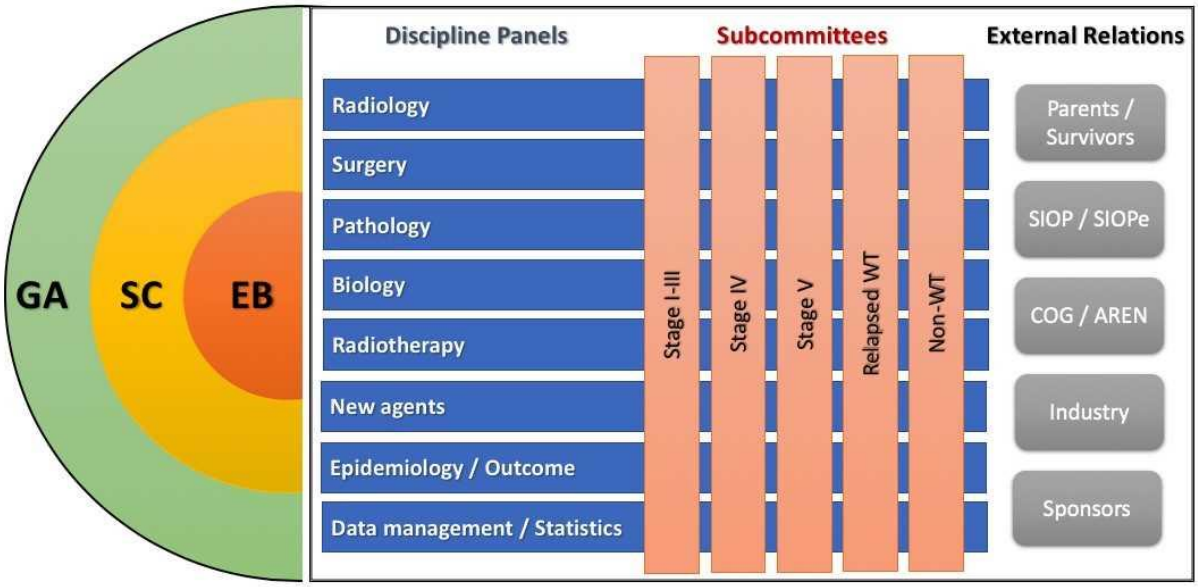

Figure 2: The structure and bodies of SIOP-RTSG. GA: General Assembly; SC: Steering Committee; EB: Executive Board; COG: Children's Oncology Group; AREN: Renal tumor trials in COG.

All discipline panels and subcommittees have gathered enormous knowledge over time, from the trials and studies and from basic research. This was based on clinical, pathological and outcome data, but also on biomaterial and imaging data. For quality control reference centers for radiology, surgery, pathology and radiotherapy were set up and which contributed immensely to current knowledge in renal tumors in childhood. This knowledge from retrospective research projects was (Table 1) and will be prospectively validated in upcoming trials and studies.

Discipline	**Findings**	**Literature**
Radiology	Diffusion weighted MRI is helpful in characterizing renal tumors	(14), (15)
	Outcome of patients with CT-only lung metastasis is inferior to no metastasis	(16)
	Specific renal tumors require biopsy before preoperative chemotherapy	(17)
Surgery	Significant less tumor ruptures after preoperative chemotherapy	(1), (3), (4)
	Less operative complications after preoperative chemotherapy	(18)
	Metastasectomy is beneficial for outcome	(19)
	Nephron sparing surgery (NSS) is possible in selected unilateral WTs	(20)
	NSS is possible in 50% on both sides in bilateral cases	(21)
Pathology	SIOP histological risk-adapted classification of renal tumors	(22)
	Diffuse anaplasia in WT is a high-risk tumor feature	(5)
	Blastemal type after preoperative chemotherapy is a high-risk tumor	(23), (24)
	Complete necrotic tumors after preoperative chemotherapy are low-risk	(24), (25), (26)
Biology	1q gain and other molecular markers are of prognostic relevance	(27)
	miRNAs from blood and tumor tissue as potential biomarkers	(28), (29), (10)
	Intra-tumoral heterogeneity is important to take into consideration	(30)
	Spheroids and organoids from tumor tissue can be established	(31), (32), (33), (34)
Radiotherapy	Postoperative irradiation is as beneficial for outcome as preoperative	(2)
	Boost for positive lymph nodes is not needed	(35)
	Consensus on flank target delineation for highly conformal radiotherapy	(36)

Table 1: Most important findings by SIOP-RTSG.

The basis for the current UMBRELLA study is summarized in several reviews on Nephroblastoma,[13,37,38] relapse treatment,[39,40] pathology and biology,[41] but also on different non-WTs.[42-46]

Over the last decades collaboration and exchange of knowledge between SIOP-RTSG and the Children's Oncology Group Renal Tumor Committee has developed resulting in a number of papers such as renal tumors of early age,[47] a meta-analysis of high dose chemotherapy,[48] late relapses,[49] the advances of international collaboration[50] and new approaches to risk stratification for WT.[51] In 2015 the task force HARMONICA (HARMONIzation and CollAboration for pediatric renal tumors) was established as an exchange platform, building on the expertise of both large study groups, enhancing international collaboration and supporting Young Investigators interested in renal tumors in childhood.

Based on all these efforts we hope that the goal of SIOP-RTSG to cure every child with a renal tumor will become reality.

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