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ANNALS OF ONCOLOGY driving innovation in oncology

EDITORIAL

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

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. It was also the first solid tumor where lung metastases were successfully treated with the addition of actinomycin and radiotherapy in the early 60s. Shortly after, two study groups—the International Society of Paediatric Oncology (SIOP) in Europe, and the National Wilms Tumor Study group (NWTSG) in North America—were formed and started running prospective, randomized trials intended to find optimal treatments 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 (Figure 1). SIOP focused on the relative merits of prenephrectomy treatment in contrast to the NWTSG, which pursued immediate surgery. The recently initiated SIOP—RTSG 2016 UMBRELLA study is recruiting patients from most European countries and from the other continents.

In the first three trials (SIOP 1, 2, and 5) the benefits of preoperative 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 postsurgical treatment.[5] Duration and intensity of chemotherapy were randomized in local stages, building the basis for future trials, and less than one-third of patients had to receive radiotherapy since. In parallel, a pilot study was completed for patients with metastatic tumors, showing that a three-drug preoperative chemotherapy regimen [vincristine, actinomycin, and doxorubicin (AVD)] is efficient and allows omission of lung irradiation in >70% of patients in complete remission after preoperative 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 preoperative chemotherapy in localized WT with vincristine and actinomycin (AV) was found to be the gold standard in SIOP-9.[7] After the 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-WT stage I accounts for >50% of localized WTs, a majority of WTs is now cured with only 8 weeks of two-drug AV chemotherapy (4 weeks preoperatively and 4 weeks postoperatively) 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 high survival rates, in SIOP 2001 trial the use of anthracyclines was evaluated 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, with 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 analyzing biomaterials systematically, the goal is to find new biomarkers and better stratification parameters for future trials.[13] Furthermore, for the subgroup of patients with stage IV WT, a randomized trial will explore whether a less toxic preoperative chemotherapy with carboplatin, etoposide, and vincristine is as effective as AVD. Another trial is asking whether highly conformal radiotherapy is as effective as conventional regimens.

Since the SIOP 93-01 trial, patients with non-WTs are registered, and since the 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 on SIOP protocols (Figure 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 (Figure 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, irrespective of the tumor type, socioeconomic 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.

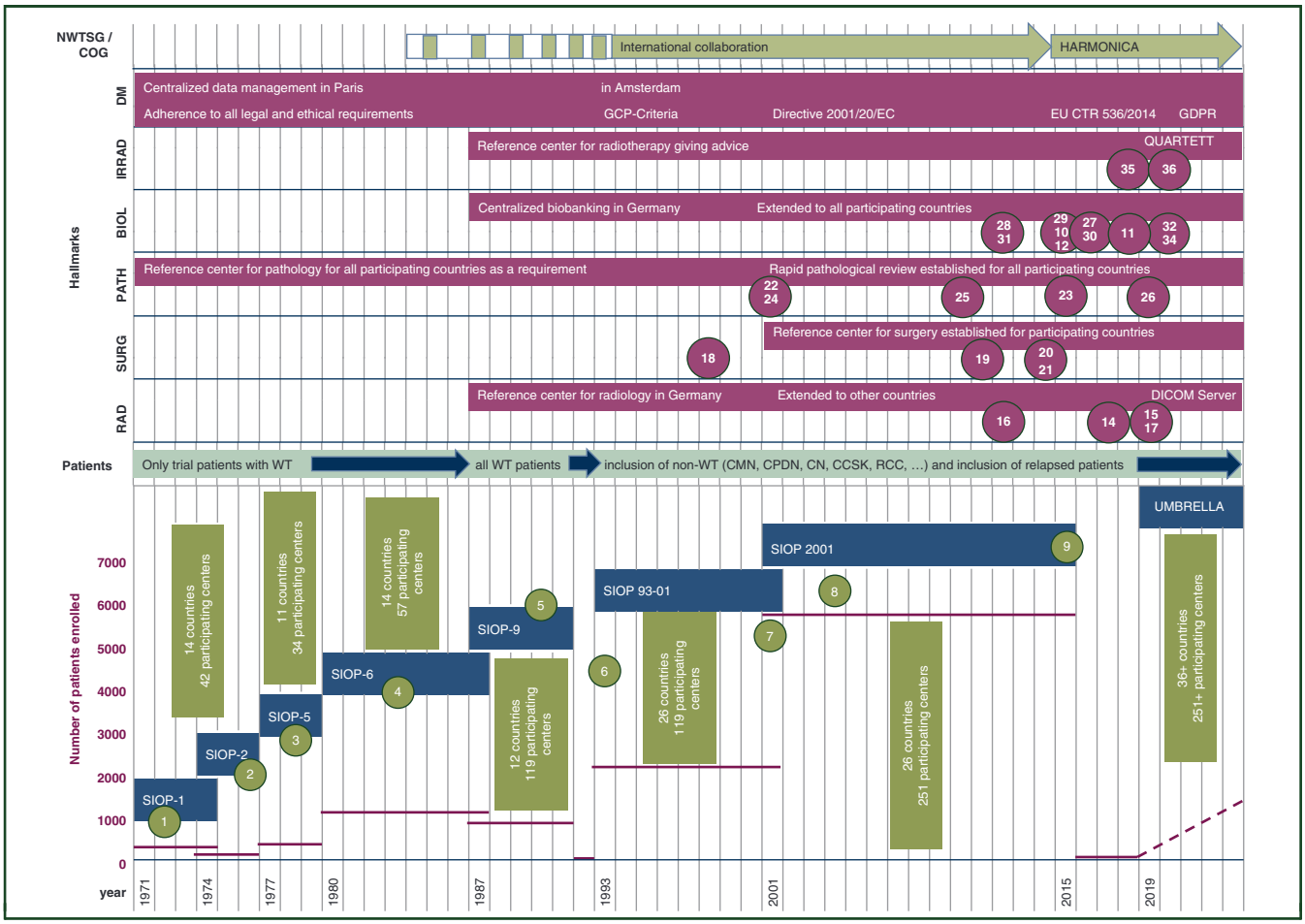

Figure 1. Clinical trials for childhood renal tumors over time.
Numbers in circles refer to the corresponding references; 2001/20/EC, Clinical Trial Directive; BIOL, biology; CCSK, clear-cell sarcoma of the kidney; CMN, congenital mesoblastic nephroma; CN, cystic nephroma; COG, Children's Oncology Group; CPDN, cystic partially differentiated nephroblastoma; CTR, Clinical Trial Regulation; DM, data management; GCP, good clinical practice; GDPR, General Data Protection Regulation; IRRAD, Radiotherapy; NWTSG, National Wilms Tumor Study Group; PATH, Pathology; QUARTETT, Platform for Radiotherapy Consultation; RAD, radiology; RCC, renal cell carcinoma; SIOP, International Society of Paediatric Oncology; SURG, surgery; WT, Wilms' tumor.

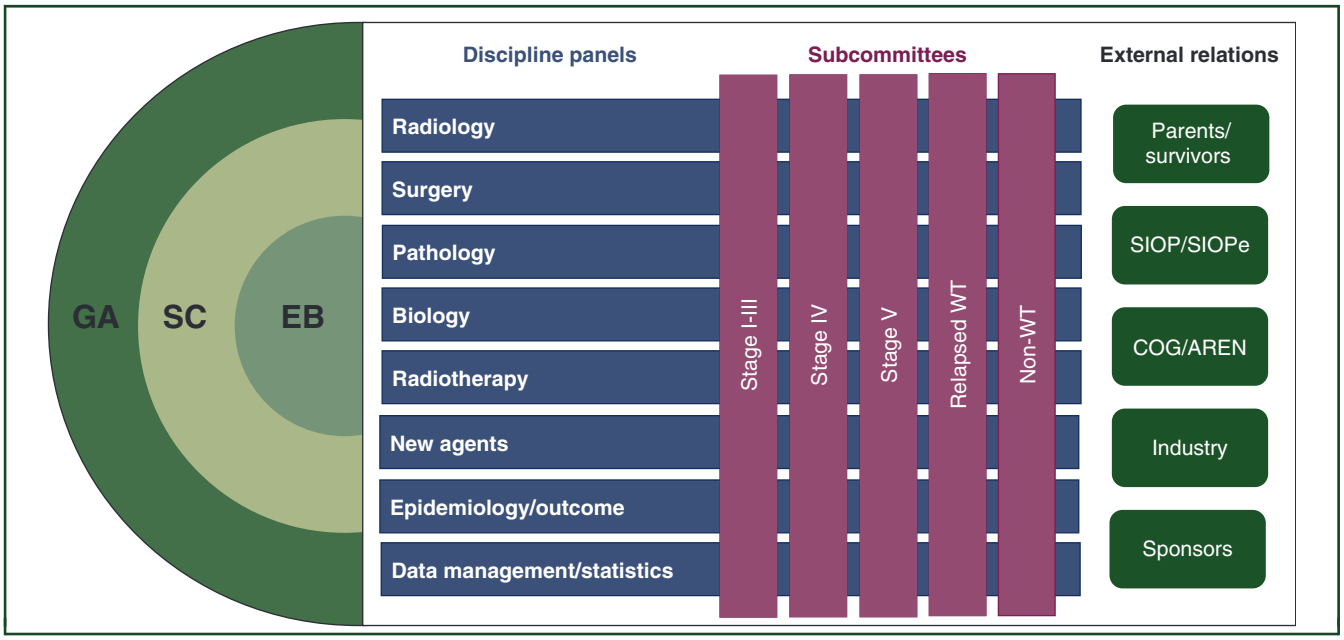

Figure 2. The structure and bodies of SIOP–RTSG.
AREN, Renal tumor trials in COG; COG, Children's Oncology Group; EB, executive board; GA, general assembly; RTSG, Renal Tumour Study Group; SC, steering committee; SIOP, International Society of Paediatric Oncology; SIOPe, European SIOP.

Table 1. Most important findings by SIOP–RTSG

Discipline	Findings	Literature
Radiology	Diffusion weighted magnetic resonance imaging is helpful in characterizing renal tumors	14,15
	Outcome of patients with computed tomography-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
	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	24-26
Biology	1q gain and other molecular markers are of prognostic relevance	27
	MicroRNAs from blood and tumor tissue as potential biomarkers	10,28,29
	Intratumoral heterogeneity is important to take into consideration	30
	Spheroids and organoids from tumor tissue can be established	31-34
Radiotherapy	Postoperative irradiation is as beneficial for outcome as preoperative irradiation	2
	Boost for positive lymph nodes is not needed	35
	Consensus on flank target delineation for highly conformal radiotherapy	36

NSS, nephron-sparing surgery; SIOP, International Society of Pediatric Oncology; WT, Wilms' tumor.

All discipline panels and subcommittees have gathered enormous knowledge over time, from the trials and from basic research. This was based not only on clinical, pathological, and outcome data, but also on biomaterial and imaging data. Quality control reference centers for radiology, surgery, pathology, and radiotherapy were set up and contributed immensely to current knowledge in renal tumors of childhood. This knowledge from retrospective research projects was (Table 1) and will be prospectively validated in upcoming trials and studies.

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 have developed, resulting in a number of papers, such as that on 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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DISCLOSURE

The authors have declared no conflict of interest.

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