Foreword

I have been lucky and privileged to work with the Société Internationale d'Oncologie Pédiatrique (SIOP) panel of pathologists for 40 years. During this time, I have seen steady and remarkable progress and success in the treatment of Wilms' tumour, with an increase in survival rates from around 50 to more than 90%.

Max Wilms, a German pathologist and surgeon, hardly realized that his thesis on "Mischgeschwulste der Niere" ("Mixed tumours of the kidney"; 1899) would link his name to the most common renal tumour in children and also turn out to be an example of successful multimodal treatment. He collected nine, mostly large, tumours from children aged 11 weeks to 11 years, which were described as round cells or myosarcomas with a content of epithelial structures in which he saw the confusing similarity to the embryonic kidney. He suspected that the component he termed "round cell sarcoma" represented tumour stem cells with the potential for differentiating into mesenchyme and epithelium and proposed its origin from the "kidney blastema" and extensively discussed oncogenesis compared with renal embryology.

In the first half of the 20th century, surgical excision was the only treatment often with a fatal outcome partly due to large tumour size. An early attempt (1916) to treat an inoperable tumour had shown that X-rays could shrink a tumour and it gave initial success, but the method was not commonly used. Slowly, surgery improved and saved some children with small tumours. A general breakthrough in treatment came with advanced surgery together with irradiation and chemotherapy as reported by Sidney Farber and his group (1956), resulting in a 2-year survival rate of 81%. The next step came with the creation and contribution of two major groups, which gave an enormous impact on treatment success. The National Wilms' Tumor Study (NWTS) began in 1969, and through national and international collaboration, it collected a large number of patients and ran several clinical and randomized trials aiming to optimize treatment for various risk groups and possibly also to identify genetic risk factors. This has led to using loss of heterozygosity of 1p and 16q to stratify patients in the current Children's Oncology Group Wilms' Tumor risk stratification protocol. A cornerstone right from the beginning of NWTS clinical trials was the work of the iconic pathologist Bruce Beckwith, who firmly related histopathology to prognosis and identified tumours with favourable or unfavourable morphology. This classification is still valid for tumours without upfront treatment as NWTS never adopted this mode until recently in some clinical settings. Among his enormous contributions, the documentation and clinical importance of nephrogenic rests must also be mentioned.

In Europe, a small group of dedicated French doctors started a paediatric oncology club in 1961, which in 1969 transformed to SIOP. At first a bilingual society, but with the intention

of becoming international, it soon had members from all over Europe, and today, with members from all over the world, it warrants the English name International Society of Pediatric Oncology ("SIOP" still used reflecting the origins). It must also be mentioned that SIOP is dovetailed with United Kingdom Children's Cancer Study Group (UKCCSG) and the German organization, The Society for Paediatric Oncology and Haematology (GPOH). They share committee and panel members, as well as general rules for treatment and results, with a hub for statistics in Amsterdam although having different national offices.

From the first study in 1971, preoperative treatment was given to children >6 months to reduce operative rupture by shrinking and encapsulating the tumour and thereby lowering the stage level. Initially, radiation was used, but in a subsequent study, it was shown that preoperative two-drug chemotherapy was as efficient as radiotherapy. This became the standard in the SIOP protocol for the treatment of renal tumours in children. An added bonus was that the responsiveness to chemotherapy was revealed by reduced tumour volume, as well as the extent of regression seen at the pathological examination. Regressive changes were a challenge for us in the pathology panel, which I joined in 1973. The dilemma was how to assign risk group or grade tumours based on the amount of regression due to chemotherapy and to relate it to the different viable components. The main issue during the first studies was to register the amount of all these elements, which later led to the three-tier risk classification in SIOP 9301 trial and study. This was updated to "the revised SIOP working classification" used in the latest study (SIOP 2001) with the important change of placing the blastemic subtype in the high-risk group. Staging was also necessary to adapt to regression, a deviation from pure anatomical grounds. Compared with the straightforward grading and staging of nonpretreated tumours, there are quantitative histological threshold values, which sometimes are difficult to interpret and make high demands on local pathologists and also make access to reference pathology important. The SIOP risk classification, however, has shown to be of significant value for distinguishing between low-, intermediate-, and high-risk tumours. The guiding light for all these trials and studies was not only to titrate the optimal amount and type of chemotherapy and irradiation but also to lower the intensity or exclude components when possible in defined risk groups to reduce toxicity but retaining cure.

Over time there has been an increasing demand to find biomarkers for those tumours that are resistant to chemotherapy, markers which are not obvious with conventional histopathology. After recognition of the mutation in the *WT1* gene led to intensive molecular research, this field has expanded at a pace which is beyond keeping up with for an old histopathologist without at least one foot in molecular research. This new constellation of clinically active doctors will be evident in the present issue. It is noteworthy that this research now focuses on normal kidney embryology to relate it genetically to Wilms' tumour development, exactly what Max Wilms also was doing with the help of a light microscope more than a hundred years ago.

In this book, you will find selected topics that cover the most recent developments spiced with some new findings in pathology, clinical management, and biological research in Wilms' tumour based on what has been achieved by a long row of hardworking devoted individuals in the large international collaborative groups. I have been fortunate to work with, and meet, most of these extraordinary persons. Some sadly passed away, some retired but most still active and found among the authors here. Enjoy their important effort!

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