Pediatric Oncology

Dominik T. Schneider · Ines B. Brecht
Thomas A. Olson · Andrea Ferrari *Editors*

Rare Tumors In Children and Adolescents

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Preface

If you work on frequent cancers, do randomized trials!
If you work on rare cancers – FIND FRIENDS!

Pediatric cancers are rare events when viewed in the backdrop of all cancers. And within the scope of childhood cancers, there are more infrequent tumors that pediatric oncologists would classify as "rare pediatric tumors." Therefore, what is the point in working on a book that specifically focuses on cancers that are "almost never" diagnosed? The most important reason may be the child who suffers with a specific tumor and the families of these children not knowing how to cope with these diagnoses.

In fact, rare cancers as a group are not as uncommon as their designation may suggest. They contribute to at least 5% of all childhood cancers. However, caring for children with such rare cancers requires a tremendous effort, primarily because sufficient information on diagnosis and therapy is missing. This book attempts to fill this information gap, by providing pediatricians, pediatric oncologists, and pediatric surgeons all currently available information required for diagnostic assessment and therapy of such patients. This book includes checklists for diagnostic procedures and detailed information on multimodal therapy of rare cancers. Thus, we hope that this book will find the interest of the international audience and will be taken to hand often, rather than rarely.

Advances in pediatric oncology have always been facilitated through sharing information and networking between experts. Networks first began among groups of institutions. Later, networks were developed on a national basis, fostered by national cooperative groups. Recently, more and more international pediatric collaborations have been established to advance prospective therapeutic trials for "more common pediatric cancers." However, since rare tumors present with extremely low incidence, international collaboration is even more essential for these patients. Otherwise, each patient with a rare tumor will remain a "first patient" that cannot benefit from experience gathered from other patients with the same diagnosis.

Therefore, we are proud that in many aspects this book reflects the growing international collaboration in the field of rare tumors. For most chapters, authors from different national study groups have shared their knowledge and developed common recommendations. For some entities, these chapters represent the first comprehensive review in this particular entity to date. Sometimes, this has been a slow and stepwise but finally successful process. The discussions have also provided a fruitful and fantastic learning experience. We hope it may provide a framework for future evolution into internationally accepted guidelines. Finally, this book is also the result of better understanding, deeper collaboration, and growing friendship.

We would like to thank all authors for their tremendous effort in writing their chapters. We would also like to thank Springer for the opportunity to develop this project. Last, we thank our families for their continuous and loving support and their patience.

Dortmund, Germany — Dominik T. Schneider
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Part I

Introduction: Rare Cancers – A Different Perspective on Oncology

Rare Tumors: A Different Perspective on Oncology

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1.1 What Defines a Rare Tumor?

Compared to cancer in adults, childhood cancer is rare, accounting for significantly less than 1% of all cancer diagnoses. Since increasing age constitutes a significant risk factor for the development of cancer, it is supposed that the overall prevalence of cancer will continuously increase while the average life expectancy rises. In contrast, birthrates are declining in most western countries, thus leading to a further decline of the overall incidence rate of childhood cancer. Thus, the question arises, what will define a rare tumor in childhood and adolescence, if the overall numbers are generally low. Is a rare cancer defined only by incidence numbers, or do specific clinical, pathological, or biological characteristics define a tumor to be rare?

A meaningful clinical definition of a rare childhood cancer has to be developed in the context of the development of childhood cancer therapy over time. The successful treatment of children has been a remarkable accomplishment of the last 40 years. Today, approximately 75% of children diagnosed in the USA or in other countries with highly developed health care systems can be expected to be "cured" (Smith et al. 2010). This has been accomplished through extensive scientific exploration and the development of national and recently, increasingly more international clinical trials through National Cancer Institutes and national and international cooperative study groups. Fortunately, these successes have at least in parts been translated into treatment strategies, suitable and assessable for children in countries with limited economic resources.

Most early pediatric clinical trials had been conducted as national studies. This strategy worked well for leukemia, the most frequent malignant neoplasia in

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childhood. Other cancers, with lower incidence, would require studies that might be conducted by several national groups. Slowly, collaborations evolved which incorporated several national groups into consortia. These alliances were necessary to allow randomized trials that could be completed in a reasonable period of time. Studies for Ewing's sarcoma and osteosarcoma are two such examples in which international collaborations has allowed development of randomized clinical trials, that would have been impossible on a national basis.

However, there is a hierarchy in the studies of childhood cancers. Most pediatric clinical trials involve childhood cancers that are relatively more common than other childhood cancers. More frequent cancers are "charted," whereas the rare, infrequent cancers are often not registered or reported. Some cancers, though "rare," have been studied well, but much more can still be done. Hepatoblastoma and germ cell tumors are examples of rare tumors that have established studies (Mann et al. 2000; Ortega et al. 2000; Gobel et al. 2002; Cushing et al. 2004; Perilongo et al. 2004, 2009). Still others continue outside current pediatric clinical trial structures. In a clinical and scientific perspective, these rare cancers might be classified as orphan diseases, indicating that no clinical structures have been developed to aid in diagnosis and treatment. There are also many cancers that are common in adults, yet infrequently seen in children. For some of these cancers, no specific clinical studies have been designed, but patients have been treated according to the corresponding guidelines for adult patients. From a clinical perspective, one could characterize them again, as orphan diseases.

Figure 1.1 illustrates the different epidemiological patterns of rare childhood cancers. There are some tumor types (Fig. 1.1a) that are defined by their generally extremely low incidence; nevertheless, they constitute characteristic tumors of childhood that are not diagnosed in adult patients. Well-defined examples include pancreaticoblastoma (see Chap. 35) or mesoblastic nephroma. In contrast, other types (Fig. 1.1b) may be diagnosed both during childhood and adolescents. Clinically and pathologically, they may be undistinguishable; however, molecular genetic studies may reveal biological differences, as it has been demonstrated, e.g., for germ cell tumors during in children and adults (for details see Chap. 39) (Schneider et al. 2004).

As mentioned above, some characteristic adult cancers, such as colon cancer or malignant melanoma, may also be diagnosed during childhood and adolescence (Fig. 1.1c). In general, this epidemiological pattern is characterized by a continuous increase of incidence over age. Thus, these rare childhood cancers constitute the left edge of the Gauss distribution curve of a frequent adult cancer. However, it should be noted that such cancers may also show biological and clinical characteristics that may distinguish such patients from others. Breast cancer and malignant melanomas are good examples. Both are frequent cancers in adults but infrequent in children and adolescents, and their presentation in young patients may be different from that in older patients (see Chaps. 41 and 10.2). Moreover, among young patients, there is a relatively higher proportion of patients with hereditary cancer syndromes (see Chap. 6). Therefore, it is not speculative to postulate that in some cancer types there may be a specific sub-entity of a rare childhood cancer hidden in the left edge of the Gauss distribution curve of a specific adult cancer (Fig. 1.1d).

These theoretical considerations illustrate that epidemiological investigations constitute the basis of our understanding of rare cancers. Most of our information on these "rare" tumors comes from national data sources such as Surveillance Epidemiology and End Results (SEER) database of the US National Cancer Institute (Ries et al. 1999), the German Childhood Cancer Registry (Schneider et al. 2004), or other national and international registries. In the following chapters, we will attempt to define "what constitutes a rare pediatric tumor in a both epidemiological and clinical sense" and discuss the diagnoses and possible treatments. This book will focus on both rare pediatric cancers that are indeed pediatric cancers and cancers that commonly occur in adults, but only sporadically in children. The difficulties in diagnosis and treatment of rare cancers will be emphasized.

The first question to be addressed is what constitutes a "rare" disease in an epidemiological understanding? The National Institute of Health in the USA defines a rare or orphan disease, as one with a prevalence of fewer than 200,000 individuals in the United States (http//rarediseases.info.nih.gov). They do clarify that subpopulations within a disease could also be considered rare. Under this definition, when compared to childhood cancer, common epithelial cancers that are diagnosed in adults would be considered a "rare" disease. One example is prostate cancer, which, despite

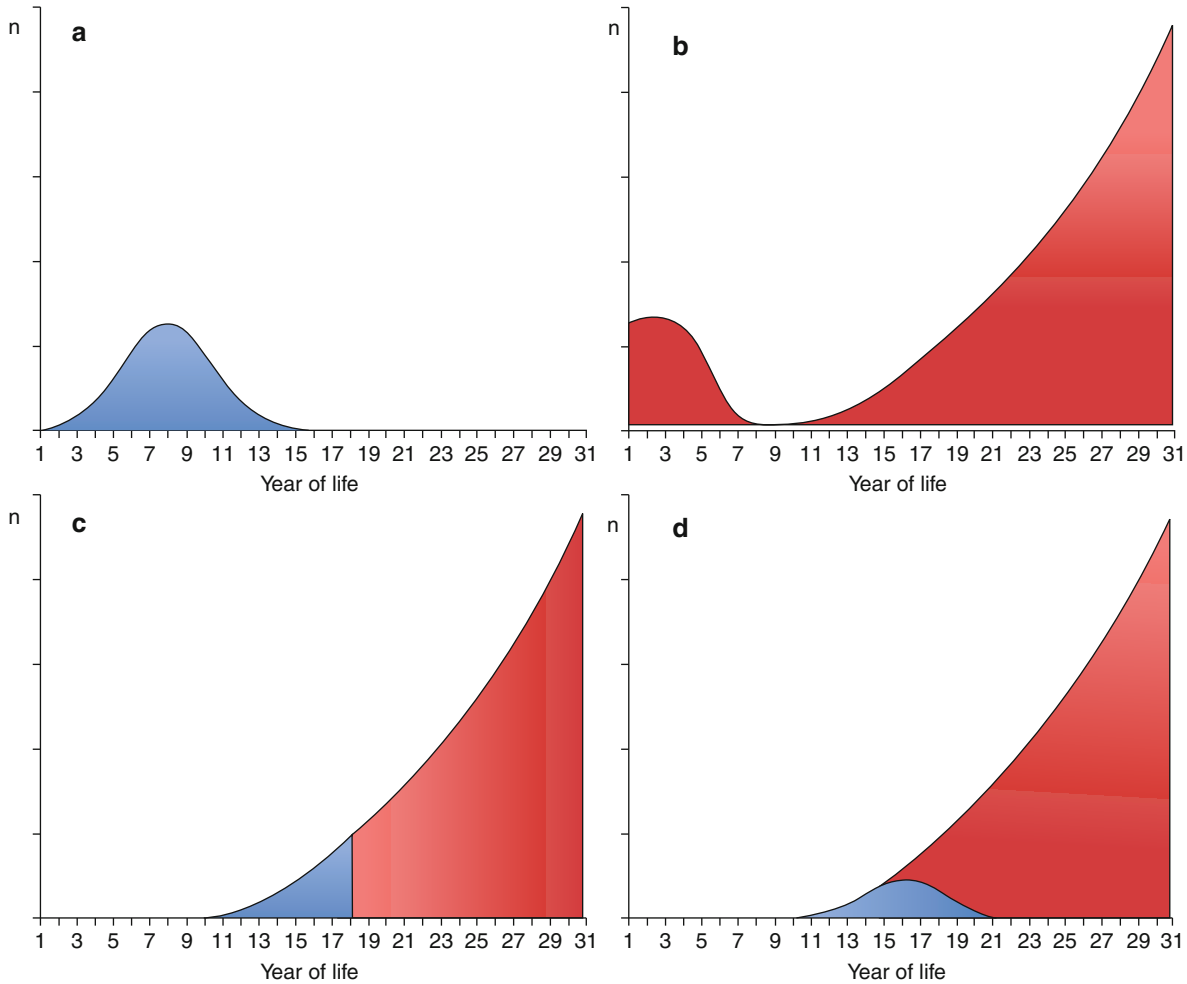

Fig. 1.1 Epidemiological patterns of rare childhood cancers: (**a**) low incidence tumor entity occurring exclusively in children. (**b**) a tumor entity with bimodal age distribution and age-dependent biology. (**c**) an adult-type tumor entity with rare occurrence during childhood and adolescence. d: an adult-type tumor entity with rare occurrence during childhood and adolescence but with distinct biology

more than 200,000 new diagnoses per year in the US, has been designated a "rare" disease towards which more funding should be directed. Of note, only 10,400 new cancer diagnoses are expected in 2010 among children up to 15 years of age in the USA (Table 1.1).

Regardless of the difficulties in comparing age-related and absolute incidence data for cancers in children and adults, it is obvious that the absolute number of childhood cancers, as detailed above, is dwarfed by the incidence of most adult cancers. Nevertheless, the individual impact on life expectancy is highest in children in which a cancer diagnosis shortens life expectancy by approximately 70 years compared to 9 years in prostate cancer. Thus, cancer remains the number one health-related cause of death in children beyond the neonatal period.

The National Cancer Institute in the United States and other national cancer funding in other countries have long recognized the importance of successful treatment of childhood cancer and supported clinical trials in pediatric cancers. Pediatric groups have received sufficient support to make outstanding improvements in the survival of childhood cancer patients.

National pediatric groups have always understood that it was also their responsibility to care for children with "rare" tumors and to study the behavior of these childhood cancers. However, they have been slow to design studies for such infrequent tumors, and most of