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. 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 50 years. Today, approximately 75% of children diagnosed in countries with highly developed healthcare systems can be expected to be "cured" (Smith et al. 2010). This has been accomplished through extensive scientific exploration and the development of collaborative national and international clinical trials. Evidence from these trials has been incorporated into treatment strategies, suitable and assessable for children in countries with limited economic resources.

While most early pediatric clinical trials were conducted as national studies, collaborations have evolved which have incorporated specific disease members of several national groups into consortia. These alliances were necessary to allow randomized trials that could be completed in a reasonable period of time. Examples include Ewing's sarcoma and osteosarcoma trials, as well as current germ cell tumor and hepatoblastoma trials.

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. Hepatoblastoma and germ cell tumors are examples of rare tumors in which national studies have led to established international collaborative clinical trials (Mann et al. 2000; Ortega et al. 2000; Göbel et al. 2002; Cushing et al. 2004; Perilongo et al. 2004, 2009). Other infrequent childhood cancers were often not registered or reported. However, there have been significant recent advances in the study of these cancers with the emergence of collaborative groups. An excellent example is the European EXPeRT collaboration (Ferrari et al. 2019). After establishing a consensus for joint actions, the EXPeRT group have subsequently published collaborative articles on mesothelioma (Orbach et al. 2020), sex cord stromal tumors (Schneider et al. 2021), and pleuro-

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pulmonary blastoma (Bisogno et al. 2021). From 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. This phenomenon increases as children age through adolescence into young adulthood. 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. 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 Chaps. 28 and 35) or mesoblastic nephroma. In contrast, other types (Fig. 1.1b) may be diagnosed during both 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 in children and adults (for details see Chaps. 31 and 39) (Schneider et al. 2004).

Adult cancers, such as colon cancer and malignant melanoma, may also be diagnosed during childhood and adolescence (Fig. 1.1c). In general, this epidemiological pattern is character-

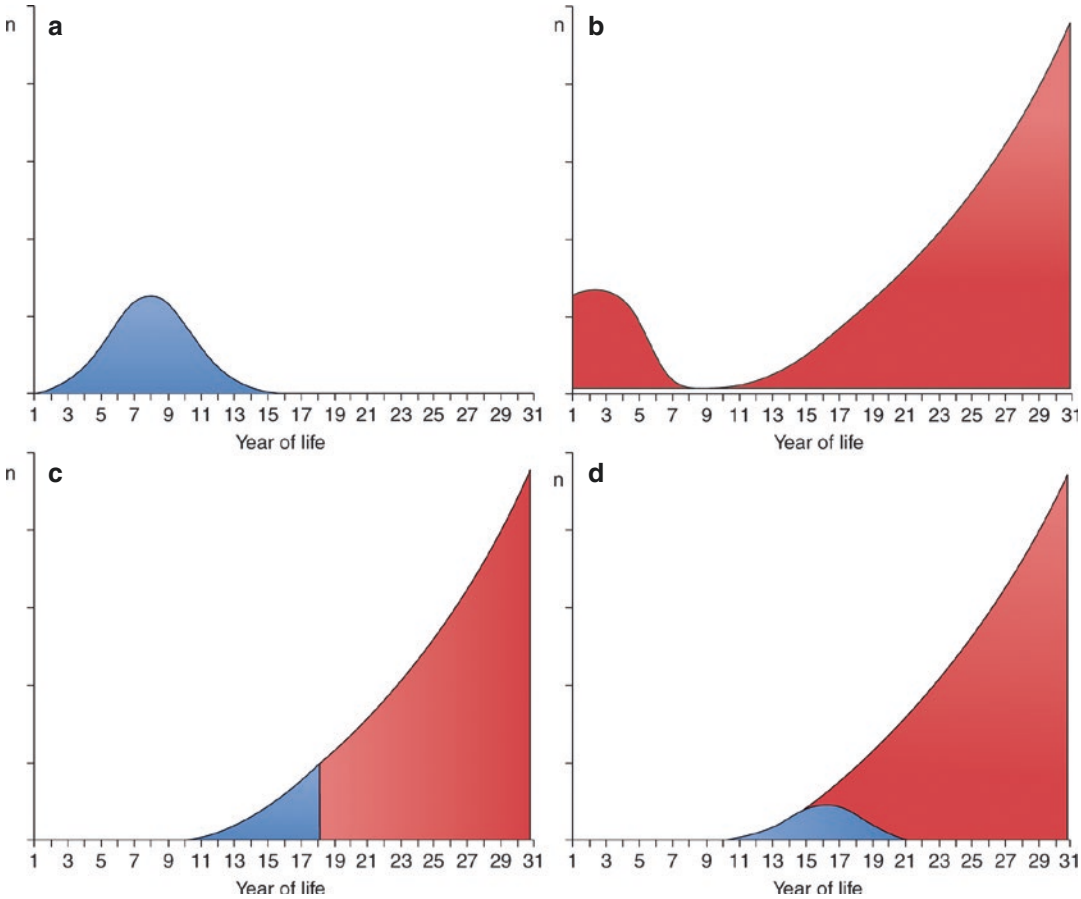

Fig. 1.1 Epidemiological patterns of rare childhood cancers: (**a**) low incidence tumor entity occurring exclusively in children. (**b**) A tumor entity with bimodal age distribution and age-dependent biology. (**c**) An adult-type tumor entity with rare occurrence during childhood and adolescence.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

ized 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. 33 and 40). Moreover, there are increased realization and identification of hereditary cancer and cancer predisposition syndromes in young patients (see Chap. 64).

Epidemiological investigations have formed the basis of our understanding of rare cancers. Most 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, disease-specific registries (Schneider et al. 2004), or other national and international registries. The advancement of molecular profiling may enhance our understanding of these rare pediatric cancers. This book will focus on both rare pediatric cancers and cancers that commonly occur in adults, but only sporadically in children. Difficulties in diagnosis and treatment will be emphasized.

The first question to be addressed is what constitutes a "rare" disease? The National Institutes of Health in the USA defines a rare or orphan disease as one with a prevalence of fewer than 200,000 individuals in the USA (https://rarediseases.info.nih.gov). Subpopulations within a disease may also be considered "rare." In addition, the National Cancer Institute in the USA defines a "rare" cancer as one with an incidence less than 15/100,000 individuals. 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).

Though the incidence of childhood cancers is dwarfed by the numbers of most adult cancers, 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.

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. But the

Table 1.1 Incidence of selected cancer diagnoses in adult patients compared to age-related incidence rates of children and adolescents up to 19 years

Adult cancer		Childhood cancer	
Histology/site	Incidence (2003–2007)	Histology/site	Age-related incidence (2003–2007)
Resp. system/lungs	66.8	Leukemia	47.4
Digestive tract	87.0	Lymphoma	23.8
Breast (women)	152.9	Brain	41.4
Genital tract (women)	25.8	Neuroblastoma	10.2
Genital tract (men)	163.4	Gonadal tumors	11.6
Urinary system	36.0	Soft tissue	12.2
Skin	21.9	Bones	8.6
Endocrine system	10.9	Nephroblastoma	7.4
Oral cavity/pharynx	10.4	Thyroid	6.4
Soft tissues	3.2	Skin	5.8
Bones and joints	0.9	Others	5.1
Brain	6.5		
Lymphoma	22.4		
Leukemia	12.3		
Total	461.6	Total	183.2

Data from the US-SEER registry (http://seer.cancer.gov/csr/1975_2007/results_merged/sect_01_overview.pdf; http://seer.cancer.gov/csr/1975_2007/results_merged/sect_29_childhood_cancer_iccc.pdf)

development of clinical trials for infrequent childhood tumors has been limited. As a consequence, *the definition of a rare cancer in childhood does not simply reflect the low incidence but mainly refers to its status as an* "*orphan disease*." No standardized diagnostic and therapeutic guidelines are available to ensure that each patient is treated on an individual basis. For many of the more common childhood cancers, sophisticated risk stratification has led to further improvement of therapy. Many patients are treated on an individualized basis, determined by evidence-based risk assessment. But in rare pediatric cancers, limited risk assessment and treatment data are available. Therefore, networking, as demonstrated by the European EXPeRT Group, has as its goal the improved exchange of experience (and data) providing a method to increase understanding of these rare tumors. Finally, limited research opportunities exist for such rare cancers. This limits opportunities to collect further data that might speed up development of improved therapies. Current collection methods might not provide data on the true incidence of these tumors. Perhaps, the encouraging experience that has been gained with collaborative rare tumor groups might provide new perspectives for scientific evaluation and the development of guidelines based on better evidence.

1.2 The Issue of Adult Cancers in Children

Many adult cancers occur very infrequently in children. Gastrointestinal cancers, melanomas, lung cancer, breast cancers, and head and neck carcinomas cause millions of deaths each year. Yet, they are exceedingly rare in pediatric-aged patients. Nevertheless, parents and pediatric healthcare providers must be aware that these tumors can affect children because these children are rarely referred to a pediatric oncologist.

The question "Do adult-type cancers found in children have the same biological characteristics and behavior of the same cancer, isolated from an adult patient?" should be addressed (Ferrari et al. 2005). Are melanomas or epithelial cancers in children and adults the same disease? There are even more very important questions: "Why and how do pediatric patients develop adult tumors in a very short time period compared to protracted development in adults?" "Do they also develop through precancerous stages, as it has been extensively described, e.g., for intestinal polyps and colon carcinoma?" "How may these tumors arise in the obvious absence of environmental carcinogens such as ultraviolet light, tobacco smoke, asbestos, or others?"

One hypothesis is that pediatric tumors, which are classified as an adult-type tumor, such as adenocarcinoma of the colon, may not be biologically comparable to the histologically identical tumor in elderly patients. For some tumors, this hypothesis may be supported by different response rates to chemotherapy (e.g., gastrointestinal stromal tumors, GIST; see Chap. 27) (Demetri et al. 2006; Janeway et al. 2009). In this situation, pediatric patients would be expected to have decreased response rates when compared to adult patients. It is essential that if you administer treatments that have had success in adult patients, you collect data to support the hypothesis that this particular treatment will also save pediatric patients' lives.

In other entities, such as testicular and extragonadal germ cell tumors (GCT), different biological subgroups according to age have been clearly defined by genetic and molecular genetic analyses (see Chaps. 31 and 39). Even more importantly, there are well-defined biologic differences despite identical histology, e.g., yolk sac tumor. Of note, these biological differences may also translate into prognostic stratification, e.g., of mediastinal germ cell tumors according to age.

Comparable studies need to be performed for other adult cancers rarely occurring in children. However, such genetic studies have been hampered by the limited availability of appropriate tissue samples of these rare tumors. Therefore, central collection of tissue samples from rare tumors in central registries should strongly be advocated. This measure would provide researchers with the opportunity to advance the molecular understanding of rare cancer entities, with immediate impact on clinical diagnosis and follow-up

(e.g., association of DICER1 mutations in pleuropulmonary blastoma and Sertoli-Leydig cell tumor (Hill et al. 2009)) and maybe even options for targeted treatment (C-KIT mutations in gastrointestinal stromal tumors (Demetri et al. 2006; Janeway et al. 2009)).

1.3 Clinical Issues in the Diagnosis and Treatment of Rare Pediatric Tumors

Rare pediatric tumors pose many challenges to pediatric oncologists. Some rare tumors, such as hepatoblastoma and GCT, are well known to pediatric oncologists. Pediatricians are also familiar with these tumors, even if they have never seen a patient with hepatoblastoma or GCT. However, the majority of tumors described in this book are tumors usually seen in adults. Diagnosis of these cancers in children can be difficult. Diagnostic approaches may not be familiar to pediatric oncologists. Once a diagnosis is established, treatments are often complex due to the lack of evidence to guide treatment in children. Moreover, some of the drugs or drug combinations applied in adult patients may not be familiar to pediatric oncologists, and toxicity in children has not yet been studied.

1.4 Delays in Diagnosis

Many pediatric providers may not be aware of the unusual presentations of rare tumors. An illustrative example is adenocarcinoma of the colon (see Chap. 32). Abdominal pain is a frequent complaint in children and adolescents. Most children with abdominal pain have gastrointestinal infections, and stool may often contain some blood. Another characteristic sign of adenocarcinoma of the right colon is iron deficiency. Iron deficiency constitutes another rather frequent diagnosis in children. In both situations diagnosis may be delayed. Several reports have suggested that colorectal carcinomas in children present with more extensive disease, more aggressive histiotypes, and poorer prognosis (Hill et al. 2007; Ferrari et al. 2008; Saab and Furman 2008; Sultan et al. 2010). These data may suggest that this disease may be biologically different in children (Durno et al. 2005). However, a delay in diagnosis may also contribute to the poorer prognosis. Education is important to identify patients at risk. We do have experience with screening as is well established in some childhood diseases, such as Beckwith-Wiedemann and familial polyposis (Half and Bresalier 2004; Erdman 2007). More must be done.

There are two decision points once a patient is referred for diagnosis. The appropriate laboratory and imaging studies must be completed. Diagnostic material must be acquired by appropriate surgery or biopsy. To ensure that adequate and complete material is collected for optimal diagnosis, both skilled (pediatric) surgeons and pathologists must collaborate. This expertise may be lacking at many institutions. This often results in further delays, and patients must be referred to other specialists. Patients often require subsequent surgery to collect more material.

Skilled pathologists are essential. One might require pathologists who specialize in both adult and pediatric tumors to be located in close proximity. Often, specimens must be sent to other pathologists for review, further delaying diagnosis.

Many pediatric tumors are treated on clinical trials. Central pathology review is mandated for some rare tumors such as hepatoblastoma and germ cell tumors. But for many rare pediatric cancers, central review does not exist; however it would urgently be required in order to avoid misdiagnoses.

1.5 The Challenge of Referral and Treatment

There is a great need for practical guidelines that can help physicians. Who to call, where to go, and what to do? There are few evidence-based studies because the numbers of patients are very small (Fig. 1.2). Pediatric oncologists will only

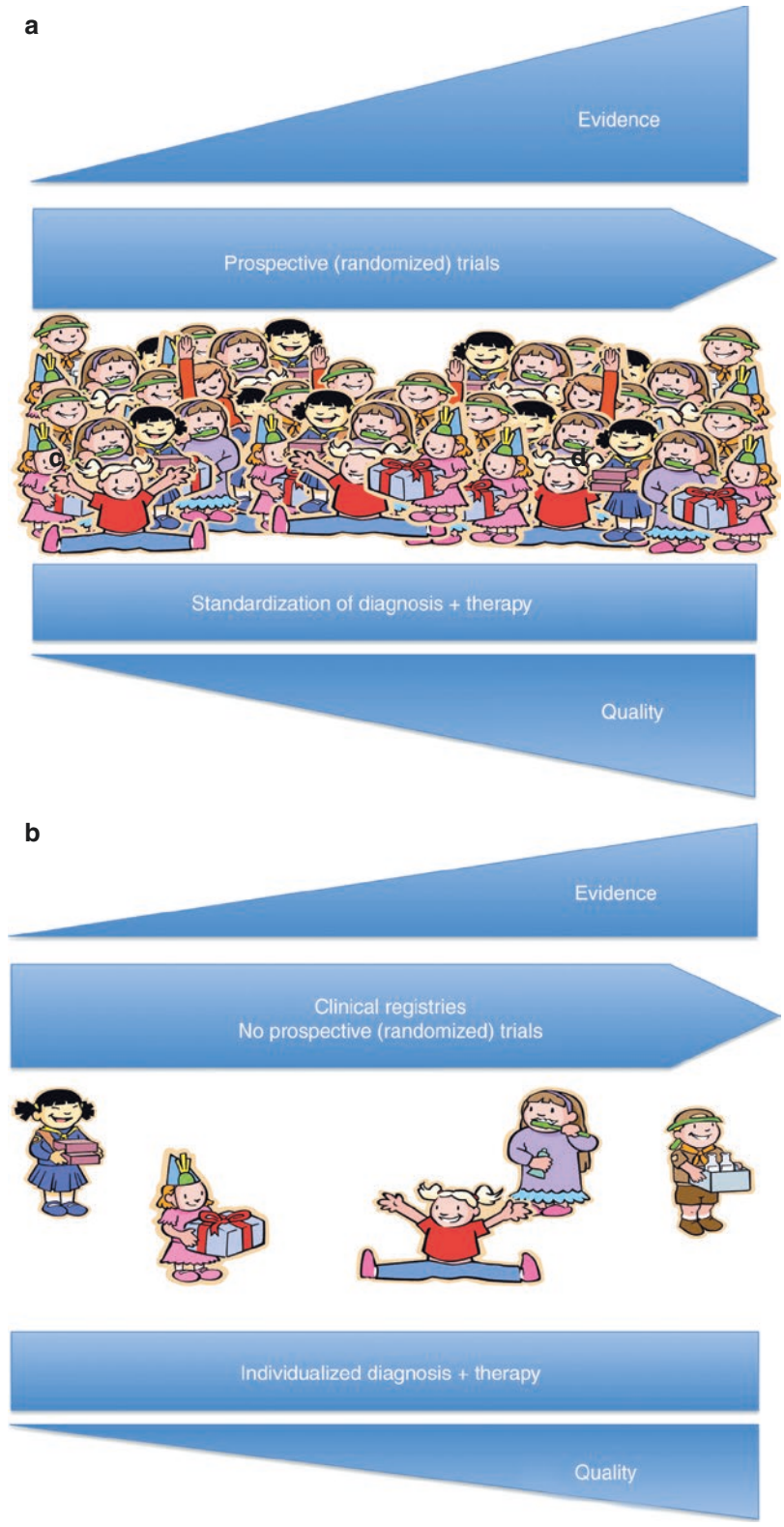

Fig. 1.2 Clinical standardization and development of increasing evidence in more frequent and rare childhood cancers. (**a**) The inclusion of large numbers of patients facilitates standardization of diagnosis and treatment. Clinical evidence is generated by the opportunity of "pattern recognition," thus identifying recurring clinical, pathological, and biological features that define prognostic and therapeutic groups. (**b**) In contrast, rare tumors are diagnosed and treated in a more individual approach. Therefore, and as a result of the low numbers, pattern recognition is impaired

manage a few patients with a specific diagnosis in their entire career.

It is crucial to develop a strategy for referral and treatment of children and adolescents with rare tumors. It is important that children and adolescents first have access to pediatric oncology treatment centers (Pastore et al. 2009). There are several considerations (Ferrari et al. 2010). There are comparison groups that, though not ideal, may be helpful. First, there are tumors that are very common in adults. Second, infrequent pediatric tumors that rarely occur in adults may also serve as a comparison group.

For children with adult-type tumors, one strategic option would be referral to an adult oncology facility. In the case of colorectal carcinoma, the presence of an experienced colorectal surgeon would seem beneficial. This might be appropriate in an older adolescent. Few pediatricians would be comfortable having a 10-year-old or even a 14-year-old treated in this manner. This may be "a good solution for the tumor, but not for the patient" (Ferrari and Sultan 2010). *Many children, both adolescents and young children, benefit from the family-focused care found in most pediatric oncology facilities*. The availability of psychologists, social workers, teachers, child life specialists, and volunteers contributes significantly to the well-being of the patients, parents, and other family members.

Another solution could be to treat these children in a pediatric setting with the contribution of experts who specialize in the treatment of adult tumors. This is often complicated by the physical separation of pediatric and adult treatment facilities. Though difficult, these obstacles have been overcome in many institutions, through collaboration at combined tumor boards, multidiscipline meetings, or clinics. Adolescent and young adult oncology centers have also been established. This collaborative strategy with medical oncologists may not always assure the best clinical management of children with adult cancers. Children are not small adults. They differ significantly from adults in physical, physiological, and cognitive functions. It is also important to emphasize that the description "child" is not uniform. Infants and old prepubertal children have immense differences in physiological, pharmacokinetic, and psychological characteristics. This knowledge and understanding of the developing child, however, is limited to the pediatrician and pediatric surgeon. One might argue that postpubertal adolescents and adults have similar physiological characteristics. However, no one would agree that their maturity and psychological states were similar. Gastrointestinal stroma tumor (GIST) in children may be one example of a complex integrated strategy. The National Cancer Institute in the USA has established a comprehensive pediatric GIST clinic that brings patients, clinicians, and scientists to the NCI clinical center for yearly study. The knowledge gained in this fashion has been very helpful in establishing that pediatric GIST differs from adult GIST. This effort benefits greatly from the strong commitment of patients, clinicians, and scientist as well as funding for NCI.

1.6 Biology

Pathological and biological studies are crucial to further success in the study of rare pediatric tumors. Clinicians and investigators must be prepared to apply new information to the study of rare pediatric tumors. This topic will be further developed in this book.

1.7 Possible Strategies in Pediatric Oncology Rare Tumors

1.7.1 Possible Solutions: "Collaboration, Find Friends!"

These tumors should no longer be viewed as "orphan" diseases, nor should they be the sole interest of small groups and experts. Rather, focused clinical/biologic studies should be promoted within the pediatric oncology community. Biology studies in pediatric rare tumors may also inform on biologic patterns in other pediatric tumors (Fig. 1.3).

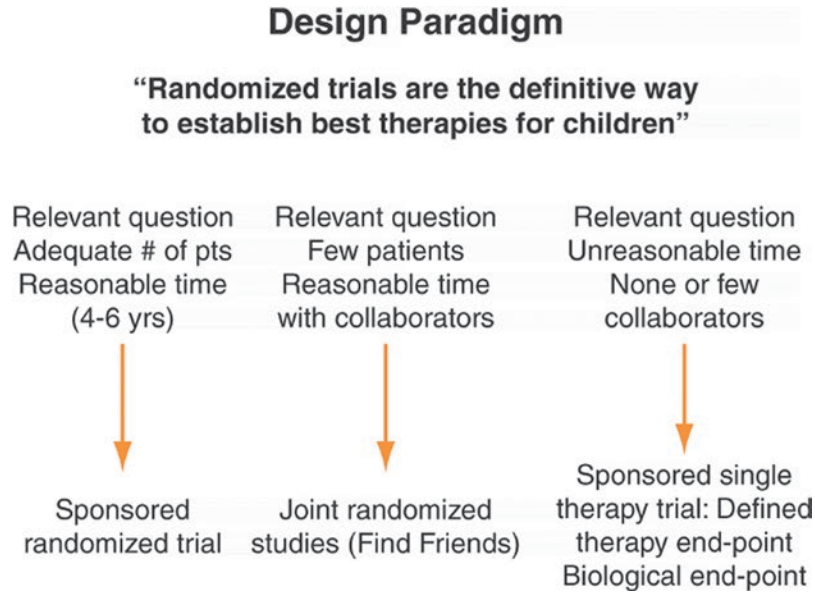

Fig. 1.3 Strategies for clinical trials in frequent and rare cancers

There have been recent movements to promote studies of patients with rare pediatric tumors. In Europe, several national groups established committees within their structures: the Italian Tumori Rari in Eta Pediatrica (TREP) (Ferrari et al. 2007) and Rare Tumor Group in the German Society of Pediatric Oncology and Hematology (GPOH) (Brecht et al. 2009). As detailed previously, the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT) has been very successful. In the USA, the Children's Oncology Group (COG) established the Rare Tumor Committee. Several collaborative groups for rare tumors, such as thyroid cancer, have also been established. Collaborations with national pediatric rare tumor groups could be established. One suggestion would be to develop specific guidelines for institutions that see only one to two new cases per year. The goal of such a study might be to collect biological specimens and minimal clinical data for correlation. These studies would require standard methodology to collect data.

It is essential that cooperative groups support efforts in advancing knowledge of rare pediatric tumors. However, these studies are hampered by lack of funding. In times of government cutbacks in research funding, priorities are established. Funding for infrequent childhood cancers may require innovative strategies.

There has been success recently in establishing clinical trials that accrue patients from childhood through adolescence, into young adulthood. Examples of these trials include leukemia, osteosarcoma, Ewing's sarcoma, and germ cell tumors. It is essential to determine a strategy for treating children and adolescents with adult-type cancers and referral institutions that have appropriate pediatric and internal medicine oncology collaboration. In addition, skilled oncology surgeons and pathologists are required.

1.8 Perspective

Despite the obstacles to the clinical management and research of rare cancers in childhood and adolescents, the field of rare cancers is one of the most fascinating aspects of pediatric oncology. Rare cancers may involve all different organ systems and many histological tumor types, including tumors of the spectrum of adult cancers. Thus, each patient broadens the perspective and deepens the knowledge of the responsible physician. In addition, the management of rare cancers poses specific challenges to the treating pediatric

oncologist who must create a diagnostic and strategic concept for an individual patient rather than completing diagnostic algorithms proposed by a checklist within a study protocol. Lastly, in the perspective of no or only limited evidence, treatment decisions must be considered extremely carefully and in truthful and intensive discussions with the patient and his family. This is only possible in a trustful relation to the patient, which, on the other hand, makes the patient "special" not only in a medical and scientific but also in a very personal sense. Therefore, the "care for the rare" may constitute a very intensive and satisfying experience.

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