Pediatric Oncology

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Editors

Rare Tumors In Children and Adolescents

Springer

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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.

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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

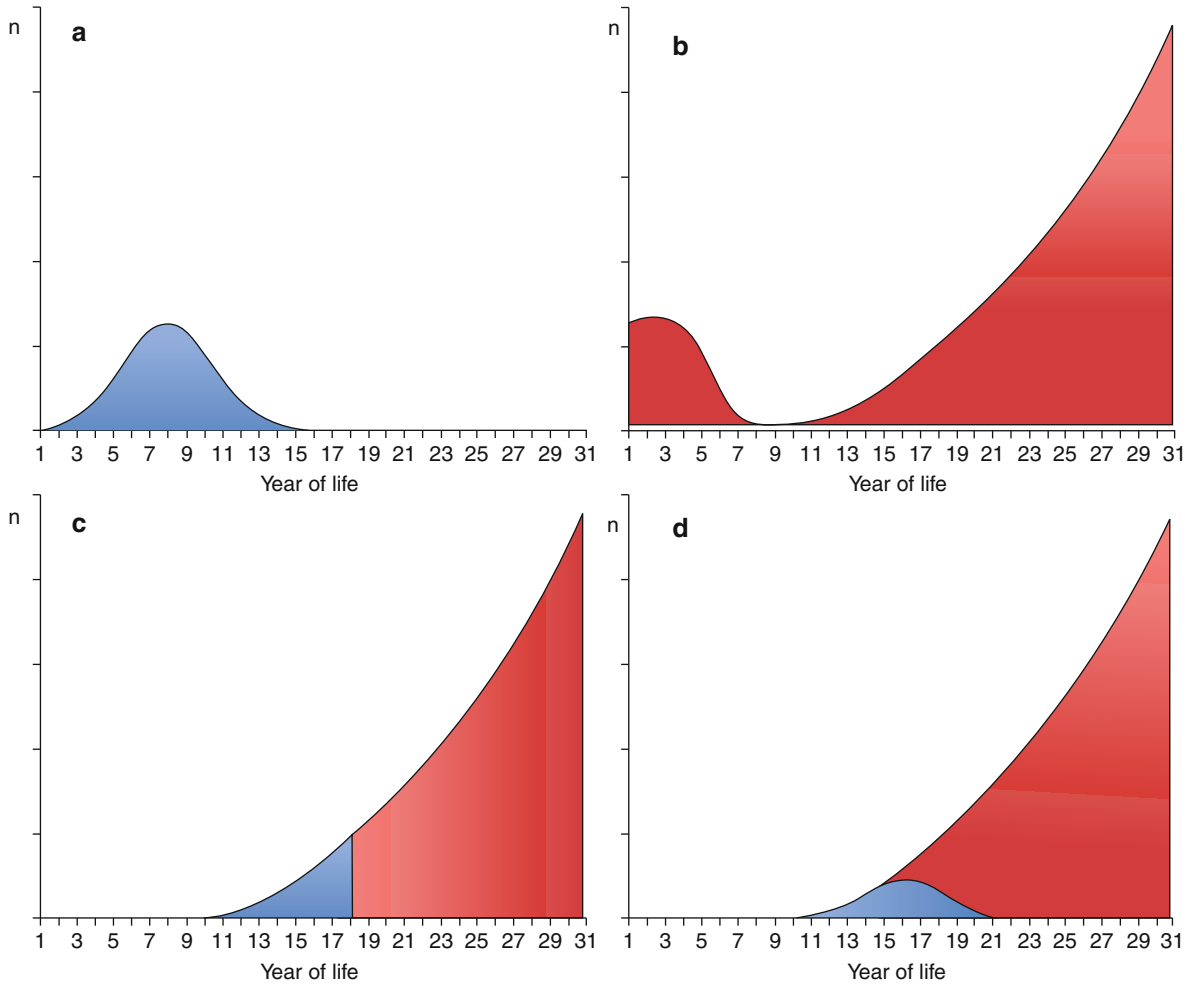

Fig. 1.1 Epidemiological patterns of rare childhood cancers: (**a**) low incidence tumor entity occurring exclusively in children. (**b**) a tumor entity with bimodal age distribution and age-dependent biology. (**c**) an adult-type tumor entity with rare occurrence during childhood and adolescence.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

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)

such rare diagnoses have been reported to clinical registries rather than prospective clinical trials. However, there are several exceptions. Clinical trials in hepatoblastoma and germ cell tumors have been conducted successfully by several national groups (Baranzelli et al. 1993; Mann et al. 2000; Göbel et al. 2002; Lo Curto et al. 2003; Cushing et al. 2004; Lopes et al. 2009). In other rare tumors, there has been a concern that unless randomized trials are possible in a reasonable time frame, studies should not be pursued. However, the same difficulties can be seen as a result of our success in more common childhood cancers such as leukemia and lymphoma. Acute B progenitor leukemia of childhood has been divided into more risk categories, such that numbers are often quite small for a particular risk stratum, thus designating it as "rare" tumor and eliminating the possibility of a randomized trial. As a consequence, low-risk acute lymphoblastic leukemia trials in the future may be single arm trials. If a reduction in therapy trial is proposed, it would require large numbers of patients. High treatment success rates in diseases, such as Hodgkin's disease, complicate trial design for statistical reasons. Nevertheless, in the world of pediatric hematology/oncology, these particular diseases are still labeled "common" and continue to stimulate research interest and to attract significant funding.

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. The quality of medical treatment of a particular patient may be compromised since only limited data for the treatment of this disease are available. Therefore, networking that has as its goal the improved exchange of experience (and data) might provide a method to increase standard of care. In addition, limited research opportunities exist for such rare cancers. This limits opportunities to collect further data that might speed development of improved therapies. Pediatric oncologists have been in the forefront of clinical trial development. Initial studies, for several more frequent pediatric cancers, have successfully advanced therapy by creating large cohorts of patients submitted to more or less uniform therapy. For many 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. However, for rare pediatric cancers, even the first step of therapy optimization remains to be taken. In fact, for many diagnoses, clinical information has only become available from clinical registries, collecting data from patients not uniformly diagnosed and treated. In the perspective of modern evidence-based medicine, however, this only constitutes a limited grade of evidence.

It is speculated, whether the current method of collecting data on these patients might be limited and the actual incidence of some tumors higher. In fact, the encouraging experience has been gained that the real incidence of many rare tumors might indeed be underestimated because they are more often underreported to clinical registries. Thus, by the introduction of clinical consultation and scientific activities, more patients than expected can be recruited, opening 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. Do they follow the hypothetical patterns described above or are they sporadic throughout childhood through adolescence? Gastrointestinal cancers, melanomas, lung and 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 health care providers must be aware that these tumors can affect children because these children are rarely referred to a pediatric oncologist.

Malignant melanoma is a specific illustrative example of the difficulty in determining an accurate childhood incidence of a particular cancer (for details see Chap. 10.2). Dermatologists suggest that melanoma is underreported in children (Strouse et al. 2005; Ducharme and Silverberg 2009). In contrast, many children have other melanocytic lesions that can be confused with malignant melanoma since rare entities such as Spitzoid nevi are difficult to define histopathologically (Pappo 2003; Cerroni et al. 2010). Many lesions in children are not biopsied and it appears that children may do well (Ferrari et al. 2005). This reflects the diagnostic problems often observed in rare tumors. Lack of experience in rare tumors presents a dilemma, which might only be overcome, by the concentration of such samples in pathologic reference centers. Unfortunately, this opportunity is often missed in rare tumors.

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. 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?"; and "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 (for example, gastrointestinal stromal tumors, GIST, see Chap. 34) (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 chap. 39). Even more importantly, there are well-defined biologic differences despite identical histology, e.g., yolk sac tumor. Of note, these biological differences 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. Lack of studies, non-withstanding, how are tumors that rarely occur in children diagnosed in a timely manner. 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. This is probably a result of education processes. However, the majority of tumors described in this book are tumors usually seen in adults. Diagnosis of these cancers can be difficult, in particular, in children. Adult cancers, which are predominately epithelial, differ substantially from pediatric cancers.

Therefore, diagnostic approaches may not be familiar to pediatricians and even 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

Rare pediatric tumors are often marked by long delays in diagnosis. Primary care physicians are the first entry point to the medical system for children with cancer. Primary care physicians may not be the only physicians who might not recognize a rare pediatric cancer. Many pediatric subspecialists, including pediatric oncologists, may not be aware of the unusual presentations of rare tumors. One 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 a rather frequent diagnosis in children. How many pediatricians would suspect colorectal carcinoma in patients with abdominal pain and/or iron deficiency anemia?

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 indeed be biologically different in children (Durno et al. 2005). However, it should also be considered to which extent delays in diagnosis may substantially contribute to the poorer prognosis. Education is important to identify patients at risk. We may not be attuned to screening pediatric patients for cancer. This is probably related to the preponderance of embryonal cancers seen in our practices. We do have experience with screening in some childhood diseases, such as Beckwith-Wiedemann and familial polyposis (Half and Bresalier 2004; Erdman 2007). Many pediatric oncology groups have developed childhood cancer survivor programs with improved screening for secondary "adult-type" cancers. More must be done.

Some health care delivery systems, throughout the world, may require several steps before the appropriate expert sees the patient. Still, there are few "true" rare tumor experts, and even if they were identified, their experience is certainly still more limited than internal medicine colleagues who are informed by data generated by prospective clinical studies. Therefore, it should be discussed, whether pediatric oncologists are indeed sufficiently trained to diagnose and treat these patients. The first impression could be that participation by internal medicine oncologist may be essential. However, as pediatricians, we are convinced that oncologic treatment of children reaches beyond the application of chemotherapy but also involves specific child and family-centered psychosocial support. This support can only be provided within pediatric oncological centers, even for adolescent patients, which have specific requirements, e.g., regarding school education.

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 insure 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 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

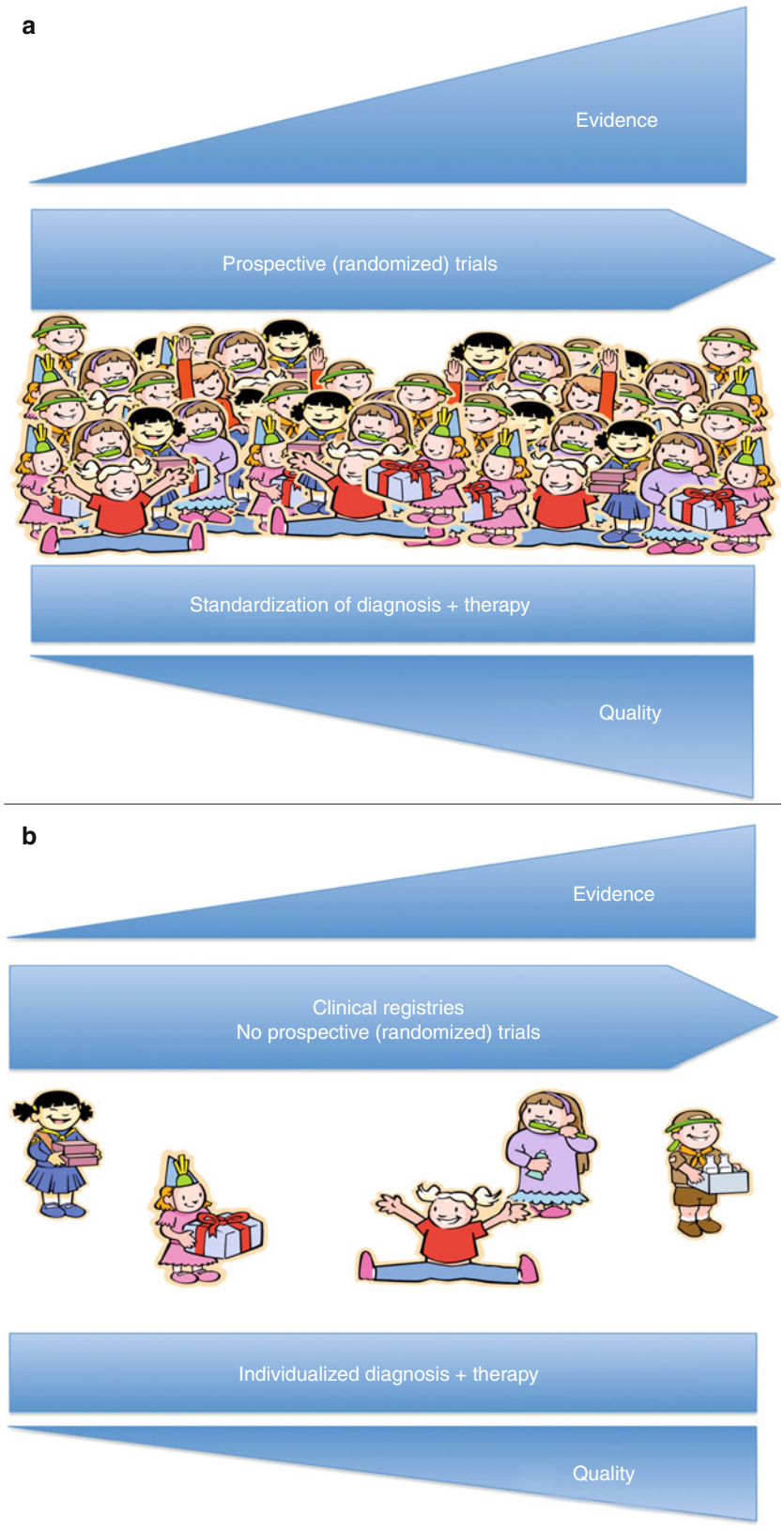

Fig. 1.2 Clinical standardization and development of increasing evidence in more frequent and rare childhood cancers. (**a**) The inclusion of large numbers of patients facilitates standardization of diagnosis and treatment. Clinical evidence is generated by the opportunity of "pattern recognition," 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

oncologists will only 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 or multidiscipline meetings and clinics. Though the best solution would be cooperation between adult and pediatric oncologists, this option still remains elusive.

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. Differences in anthropometric measures, body composition, organ size, maturity, and hormone status may directly influence the reaction between host and tumor cells, clearance of drugs, or treatment morbidity. No evidence has ever been provided that chemotherapeutic regimen primarily developed for elderly patients, e.g., with colon cancer, shows the same pharmacokinetic distribution and tumor effectiveness in adolescents. It could even be argued that adolescents are undertreated with such regimens because of increased clearance of cytotoxic drugs. These differences might restrict the application of adult treatment regimens to the treatment of children. The reverse might apply in developing adult treatment strategies when they are diagnosed with a "pediatric" cancer. Thus, it is a common observation that comparable cytotoxic regimen, e.g., for childhood leukemia, appears to be less tolerated in adolescents compared to young children.

Gastrointestinal stroma tumor (GIST) in children may be one example of a complex integrated strategy. The National Cancer Institute in 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. It is hoped that this interaction will lead to better understand and improved treatment of these patients. 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 may be crucial to further success in the study of rare pediatric tumors. As the whole genome project moves forward, clinicians and investigators must be prepared to apply new information to the study of rare pediatric tumors. This will be hampered if we do not establish a clear strategy to collect and store precious rare tumor material for future study. This topic will be further developed in this book.

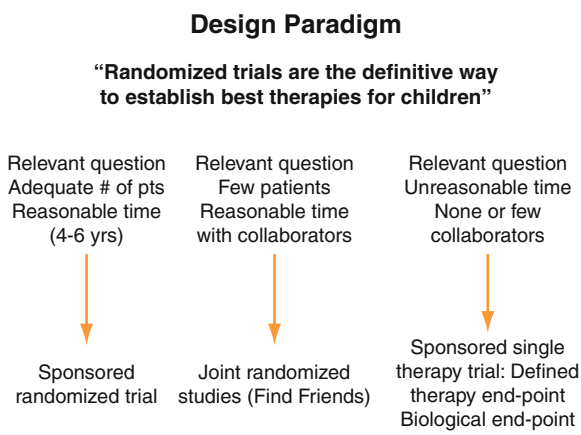

Fig. 1.3 Strategies for clinical trials in frequent and rare cancers

A strategy must be developed that includes diagnosis (biology studies included) and treatments. The awareness of rare pediatric tumors must be raised.

1.7 Possible Strategies in Pediatric Oncology Rare Tumors

1.7.1 Possible Solutions: "Find Friends!"

It seems that the new millennium may be a key time to focus on these tumors. They 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; Ferrari, 2010).

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 Pediarica (TREP) (Ferrari et al. 2007), Rare Tumor Group in the German Society of Pediatric Oncology and Hematology (GPOH) (Brecht et al. 2009), the French, British, and Polish rare tumor study groups have also worked to establish a pediatric rare tumor consortium throughout Europe (European Cooperative Study Group on Pediatric Rare Tumors, eXpert). In this cooperative group, several multinational disease specific projects have been initiated. In the USA, the Children's Oncology Group (COG) formed the Rare Tumor Committee, which includes germ cell tumors, liver tumors, retinoblastoma, and infrequent tumors. The basis for this combination was that these tumors needed to be studied with a similar strategy. The strategy includes: biology studies, well-designed clinical trials, and the recruitment of other international pediatric groups to collaborate in these trials.

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 cancers usually suffers. Pediatric cooperative groups remain the only forum for the study of rare pediatric tumors. When rare tumors studies are opened by a cooperative group, such as COG, there are still many difficulties. Few individual institutions are willing to open trials that have little or no potential for accrual. The time and cost of Institutional Review Board (IRB) approval may be prohibitive. One specific example is a recent, COG germ cell tumor trial. After approval and activation, a very slow institutional approval process took place. Expected accrual was only achieved after approximately 90/200 COG institutions had activated the protocol. It took 1 year to reach approval in 90 institutions. In contrast, COG acute lymphocytic leukemia front line trials are approved at all institutions. This illustrates that clinical research on rare tumors is less enthusiastically supported both at central funding institutions and in clinical study centers. As a consequence, the study of rare pediatric tumors is complex and investigators can often become frustrated by lack of funding and the inability to recruit cooperation partners and junior investigators to the field.

Many young investigators want to contribute to the field of pediatric oncology. The study of rare tumors is not often appealing as there are few opportunities to lead a significant study within our cooperative group structure. They gravitate to diseases where more opportunities and more mentors are available.

Collaborations with national pediatric rare tumor groups could be established. Currently, groups in USA and Europe collaborate on clinical trials for pediatric oncology. Why not establish such agreements for rare pediatric tumors? 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.

In this aspect, this book may serve as an initiation point since international experts in the field of different rare childhood cancers have collaborated to collect evidence and to agree on common recommendations and guidance.

Moreover, other networks could be modified. There have been several attempts to accrue adult patients on pediatric trials. There has been some success recently in accruing young adults on COG trials for leukemia, osteosarcoma, and Ewing's sarcoma. The accrual of COG patients on adult trials (example, melanoma) has been very disappointing.

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. In the absence of these components, should careful guidelines be established that include communicative links to referral institutions that have the appropriate support for these rare tumors?

Again, as a first step, this book tries to translate knowledge generated in adult cancer patients into the pediatric setting. Experts from the field of adult oncology have shared their knowledge with pediatric oncologist, resulting in interdisciplinary articles on specific cancer types such as colon cancer and malignant melanoma.

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. Last, 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 a very personal sense. Therefore, the "care for the rare" may constitute a very intensive and satisfying experience.

References

Baranzelli MC, Flamant F et al (1993) Treatment of non-metastatic, non-seminomatous malignant germ-cell tumours in childhood: experience of the "Societe Francaise d'Oncologie Pediatrique" MGCT 1985–1989 study. Med Pediatr Oncol 21(6):395–401

Brecht IB, Graf N et al (2009) Networking for children and adolescents with very rare tumors: foundation of the GPOH Pediatric Rare Tumor Group. Klin Pädiatr 221(3):181–185

Cerroni L, Barnhill R et al (2010) Melanocytic tumors of uncertain malignant potential: results of a tutorial held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008. Am J Surg Pathol 34(3):314–326

Cushing B, Giller R et al (2004) Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a Pediatric Intergroup Study – Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22(13):2691–2700

Demetri GD, van Oosterom AT et al (2006) Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 368(9544):1329–1338

Ducharme EE, Silverberg NB (2009) Pediatric malignant melanoma: an update on epidemiology, detection, and prevention. Cutis 84(4):192–198

Durno C, Aronson M et al (2005) Family history and molecular features of children, adolescents, and young adults with colorectal carcinoma. Gut 54(8):1146–1150

Erdman SH (2007) Pediatric adenomatous polyposis syndromes: an update. Curr Gastroenterol Rep 9(3):237–244

Ferrari A, Sultan I (2010) When adult cancers occur in children. Expert Rev Anticancer Ther 10(11):1683–1685

Ferrari A, Bono A et al (2005) Does melanoma behave differently in younger children than in adults? A retrospective study of 33 cases of childhood melanoma from a single institution. Pediatrics 115(3):649–654

Ferrari A, Bisogno G et al (2007) The challenge of very rare tumours in childhood: the Italian TREP project. Eur J Cancer 43(4):654–659

Ferrari A, Rognone A et al (2008) Colorectal carcinoma in children and adolescents: the experience of the Istituto Nazionale Tumori of Milan, Italy. Pediatr Blood Cancer 50(3):588–593

Ferrari A, Casanova M et al (2010) Peculiar features and tailored management of adult cancers occurring in pediatric age. Expert Rev Anticancer Ther 10(11):1837–1851

Göbel U, Calaminus G et al (2002) Management of germ cell tumors in children: approaches to cure. Onkologie 25(1):14–22

Half EE, Bresalier RS (2004) Clinical management of hereditary colorectal cancer syndromes. Curr Opin Gastroenterol 20(1):32–42

Hill DA, Furman WL et al (2007) Colorectal carcinoma in childhood and adolescence: a clinicopathologic review. J Clin Oncol 25(36):5808–5814

Hill DA, Ivanovich J et al (2009) DICER1 mutations in familial pleuropulmonary blastoma. Science 325(5943):965

Janeway KA, Albritton KH et al (2009) Sunitinib treatment in pediatric patients with advanced GIST following failure of imatinib. Pediatr Blood Cancer 52(7):767–771

Lo Curto M, Lumia F et al (2003) Malignant germ cell tumors in childhood: results of the first Italian cooperative study "TCG 91". Med Pediatr Oncol 41(5):417–425

Lopes LF, Macedo CR et al (2009) Cisplatin and etoposide in childhood germ cell tumor: brazilian pediatric oncology society protocol GCT-91. J Clin Oncol 27(8):1297–1303

Mann JR, Raafat F et al (2000) The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18(22):3809–3818

Ortega JA, Douglass EC et al (2000) Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. J Clin Oncol 18(14): 2665–2675

Pappo AS (2003) Melanoma in children and adolescents. Eur J Cancer 39(18):2651–2661

Pastore G, De Salvo GL et al (2009) Evaluating access to pediatric cancer care centers of children and adolescents with rare tumors in Italy: the TREP project. Pediatr Blood Cancer 53(2):152–155

Perilongo G, Shafford E et al (2004) Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology–SIOPEL 2. Eur J Cancer 40(3):411–421

Perilongo G, Maibach R et al (2009) Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 361(17):1662–1670

Ries LA, Smith MAS, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) (1999) Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program, NIH Publication No. 99–4649. National Cancer Institute, Bethesda

Saab R, Furman WL (2008) Epidemiology and management options for colorectal cancer in children. Paediatr Drugs 10(3):177–192

Schneider DT, Calaminus G et al (2004) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42(2):169–175

Smith MA, Seibel NL et al (2010) Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 28(15):2625–2634

Strouse JJ, Fears TR et al (2005) Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol 23(21):4735–4741

Sultan I, Rodriguez-Galindo C et al (2010) Distinct features of colorectal cancer in children and adolescents: a population-based study of 159 cases. Cancer 116(3):758–765

2 Showing Efficacy in Treating Rare Pediatric Tumors: Introduction to European Regulatory and Scientific Support Available to Investigators

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2.1 General Perspectives on Rare Malignant Diseases

The demonstration of safety and efficacy of a medicinal product or a medical treatment in cancer raises vastly different problems. In frequent cancer types, for example, lung carcinoma or breast carcinoma, such a demonstration is usually feasible within a short period of time, in a relatively large number of patients, although medicines' effect sizes are often modest and cure is seldom achieved despite multimodal treatment schemes.

In contrast, rare cancers discussed in this book generally create a dilemma on how to balance the small size of the patient populations with the strength of evidence that can be achieved and produced reliably. Additionally, rare tumors represent long-standing and unmet therapeutic needs, as no treatment schemes are established for many of them and, at best, only monotherapies are available.

This dilemma and the scientific challenges associated with the treatment of rare tumors have received special attention in Europe's pharmaceutical legislation and its application:

- Several European scientific guidelines are available: in oncology, on hematological malignancies, on pediatric oncology, on pediatric medicines, on small populations, and on adaptive design trials, in addition to the International Conference for Harmonization (ICH) guidance. The guidances are primarily aimed at pharmaceutical development, but can be useful to all clinical research using medicines. The paradigm is that the type of evidence that can change medical practice should be same to support the demonstration of efficacy and safety of a medicine, and

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vice versa. The guidances generally apply, irrespective of whether research is performed in pediatric or adult patients, but increasingly, the guidances produced include specific pediatric recommendations.

- In order to encourage the application of the European scientific guidances for the development of medicines, several incentives have been introduced in Europe.
- Two different types of marketing authorization were created, which can be used in situations where not all data normally included have been submitted. The conditional marketing authorization can be granted where some evidence for a positive benefit–risk balance already exists and further supportive data will be made available in the near future. The marketing authorization under exceptional circumstances can be granted where further supportive data cannot be generated because, for example, the population affected is too small to provide robust data. The two types of marketing authorizations cannot be combined for the same product. In fact, the conditional marketing authorization is changed into a regular authorization, as soon as the remaining data have been submitted. The conditional marketing authorization and the marketing authorization under exceptional circumstances are both potentially applicable to pediatric medicines. Where an authorization already existed, any additional pediatric indication becomes part of that authorization, rather than being authorized separately. Scientifically sound development generally should provide data that permit to place a new anticancer medicine into medical practice, but this is not a strict regulatory criterion for marketing authorization.

The following principal design features are often discussed for clinical trials intended to generate efficacy and safety evidence in rare tumors:

- *Patient population and inclusion criteria*: Pediatric oncology studies may include patients from different lines of treatment, having largely different previous cumulative exposures to anticancer medicines. A balance should be sought between including a sufficient number of children to obtain conclusive data in subsets from early therapeutic settings that are well-recognized in medical practice and including patients from various lines of treatment or palliative therapeutic settings. This may also be applicable to dose-finding studies, in which differences in tolerability may or may not be related to previous treatment exposures (Smith et al. 1998; Raphaël et al. 2010).
- *Efficacy endpoints*: Experience with efficacy endpoints, including time to event and response endpoints, exists since long in pediatric oncology trials. The time to event endpoints are generally applicable also to rare tumors, but the clinical importance of response may be less known in rare tumors. The progression-free survival (PFS) can be an appropriate primary efficacy endpoint in rare tumors, as tumor progression may indicate a clinically relevant symptomatic progress. For new medicines such as those with targeted or cytostatic effects, the PFS endpoint may represent a different meaning than for known cytotoxic compounds, as there may be differences in the components of PFS such as in treatment-related toxicities and deaths as well as in indicators of progression. In order to understand such differences, details of toxicities and of the treatment course after progression should be well documented. The specific guideline on PFS as primary endpoint in confirmatory trials covers further aspects including the importance of assessment schedules and the intention-to-treat principle toward censoring.[1]
- *Controlled or uncontrolled*? A dilemma is created by the well-rehearsed statement, "If the evidence is strong enough, then a randomized controlled trial is not needed." Before a trial, the size and strength of the treatment effect cannot be judged. This statement then is rarely helpful when testing a medicine with a novel mechanism of action for a rare tumor, and even less so when the tumor biology is dissimilar in adult and pediatric patients. Historical (external) controls are often considered as a substitute for internal controls, but suffer from heterogeneity (e.g., molecular diagnosis, risk allocation, treatment) particularly in rare tumors. This may make comparisons statistically unreliable, with a significant risk that the study becomes inconclusive. Medical practice evolves continually in terms of methods of diagnosis and standards of antitumor and of supportive care, with the consequence that historical controls have not received what is the best available standard of care. The standard of care normally serves as control in clinical trials, on top of

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500017749.pdf

which new medicines can be tested. If there is genuine uncertainty as to whether the standard of care is actually effective, then the best investigator's choice could be used as active comparator. Differences between trials, and between trial participants and non-participating patients, are known as trial effect. The trial effect diminishes any usefulness of external controls, although a trial effect may be less relevant for adult (Peppercorn et al. 2004), pediatric (Koschmann et al. 2010), or true population-based cancer trials. In the oncology literature, there is an ongoing debate of the usefulness of uncontrolled studies. The debate also concerns pediatric trials of infrequent malignant diseases, which are particularly criticized for their poor value in estimating a treatment effect (e.g., see Ratain 2010).

The following section presents scientific-regulatory guidelines addressing the principal design questions.

2.2 Scientific-Regulatory Guidances

The European Medicines Agency, as well as other regulatory agencies worldwide, and the International Conference of Harmonization (ICH) regularly issue guidance setting out the scientific rationale for regulatory requirements and recommendations on how to develop medicines, including how to design, conduct, and analyze clinical trials. The guidances are based on the experience gathered with successful and, maybe more importantly, with unsuccessful medicine developments.

The European Medicines Agency develops guidance on the basis of the applicable pharmaceutical legislations, and invites all stakeholders to comment during a public consultation phase. Guidances are made publicly available,[2] including guidance on evaluation of applications for Paediatric Investigation Plans (PIPs).[3] The scientific-regulatory guidances for development of medicines represent an overarching European view, independent of countries and health care systems, which each may have issued local treatment guidelines.

There are several ICH guidances which apply in particular to anticancer medicinal products, such as E6 (R1) "Guideline for Good Clinical Practice," E11 "Clinical Investigation of Medicinal Products in the Pediatric Population," E8 "General Considerations for Clinical Trials," E9 "Statistical Principles for Clinical Trials," E10 "Choice of Control Group in Clinical Trials," and E4 "Dose Response Information to Support Drug Registration." However, only the ICHS9 guideline is specific to the "Nonclinical evaluation for anticancer pharmaceuticals."

The ICHE3 guidance on the "Structure and Content of Clinical Study Reports" is of particular relevance to academic investigators collaborating with pharmaceutical companies, as it describes how to present the data that are submitted in applications for marketing authorization.

Three scientific-regulatory guidelines have been selected for the next sections. The aim is not to interpret the guidances, but rather to present the most relevant aspects, with the hope of encouraging a full reading of the documents and their application to pediatric oncology to improve the process of finding the best possible approaches and designs to investigate anticancer medicines in children.

2.2.1 Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005)[4]

This guideline was created in an effort to summarize how the most convincing evidence could be generated by trials performed in a clinical setting where only a small number of patients and potential trial participants are available. The guideline came into effect in 2007 and it not limited to a specific therapeutic area. There is no similar guidance in other regions; therefore, pharmaceutical companies may have limited experience of this guideline, if pediatric oncology trials were only conducted in the USA.

The key principle is that a prospective plan should be set out to develop a medicine. The plan should cover the design, as well as the individual and combined analyses of all studies. The medicine's effects should be explained as much as possible by the study data.

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580027549

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91#section3

[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf

Wherever possible, the plan should include collecting non-clinical data, e.g., by studying disease-specific models, dose-response relationships, and tumor dependency. The plan should aim to maximize the information from clinical trials, by prolonged follow-up, by maintaining participants in the trial even after discontinuation of the study medicine, and by balancing the trial-related burden to reduce patient dropout. Additionally, there should be attempts to explain the variability of the medicine's effect by characterizing the factors that introduce uncertainty, such as molecular target changes and associated pharmacodynamic differences, or insufficiently explored relationships of dose and treatment schedules with response. A further cause of variability observed in pediatric patients could be the dose (in-) accuracy, if an age-appropriate formulation that permits precise dosing was not used in the trial.

Some designs of clinical trials discussed in the guideline may be useful in pediatric oncology, namely those using response-adaptive methods, sequential designs, or Bayesian approaches (for design and analysis). All aim to maximize the statistical efficiency of the design. However, the guideline states that for measuring the treatment effect, a randomized controlled study with low statistical power may be preferable to uncontrolled studies.

The guideline also makes recommendations on the choice of endpoints, and how data from different sources could be collected to support a surrogate endpoint.

Excerpts of the guideline are provided in Table 2.1.

One of the main messages of the guideline is to avoid looking at pediatric oncology, in particular investigator-initiated trials in isolation. Instead, clinical trials in adult patients, the full set of non-clinical studies, and region-wide patient registries should be set out in advance in the development plan. The plan could focus on more than one medicine, to be used in sequence or in combination, or from which the best one is to be selected, and the plan should include approaches that are centered around the malignant pediatric disease.

Discussions of the plan in regulatory interactions are encouraged, as explained below, especially when alternative designs are considered, or randomized controlled trials are considered not feasible and only case series (external controls) or anecdotal case reports are available. Questions to regulatory authorities should focus for example on the choice of surrogate endpoint, any lack of randomization, or lack of control group. Although there is no defined format for such plan, the structure of Paediatric Investigation Plans[5] could be used, and developed if necessary.

The guideline on clinical trials in small populations does not mention extrapolation of efficacy. However, extrapolation could be used in a plan including well-designed studies in one population, to support the extension of efficacy results to a different target population. This may be justified if for example the target population is perhaps more vulnerable or particularly small. It is still necessary to study pharmacokinetics and safety in an uncontrolled design. Using extrapolation of efficacy is relevant for pediatric medicine development and will be discussed for the next pediatric guideline.

2.2.2 ICH Topic E 11: Clinical Investigation of Medicinal Products in the Pediatric Population (CPMP/ICH/2711/99)[6]

Two principally different situations can be envisaged when considering the development of a medicine for use by the pediatric population. Both are addressed in the E11 guideline, which came into operation already in 2001 in the regions of the ICH (Europe, United States, and Japan).

- Firstly, the condition exists in adult and pediatric populations. This should trigger considering whether efficacy in pediatric populations can be extrapolated from adult or other relevant populations. The guideline presents several criteria for deciding if extrapolation is a valid option, and it indicates how to carry out extrapolation. While extrapolation does not generate data, which on their own allow to evaluate the benefit–risk relationship, this approach may allow to reduce the number of trial participants and therefore to protect them from the clinical trial burden. Extrapolation is encouraged whenever scientifically sound and justified.
- Secondly, the condition only exists in the pediatric population without a similar disease in adults. In this case, the guideline defines the safety and non-clinical

[5] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91

[6] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf

Table 2.1 Highlights of the Guideline on clinical trials in small populations

Subtopic	Guidance text
Choice of control groups	Ideally, we wish to obtain an unbiased estimate of the effect of the treatment being investigated compared to placebo or to another active compound and, for this reason, every effort should be made to randomize patients from the beginning of the therapeutic testing phase. The goal of obtaining an unbiased estimate of the size of effect is true in studies in small populations as well as large trials for common diseases.
Use of placebo	In cases where there is no existing treatment, even in life-threatening diseases, the use of placebo as a comparator should be considered. Where a placebo control may not be possible, an appropriate control group may be "best standard of care." When other treatments are available, then an active comparator could be used as control group. However, if the active comparator does not have its own good evidence base, then superiority to that comparator will usually be necessary.
Statistical analysis and result presentation	In almost all cases, confidence intervals of estimates of the treatment effect are much more informative than *P*-values.
Intervention-response relationship	The credibility of study results may be enhanced if a dose-response relationship is seen or in cases where a chain of events can be identified (for example, drug exposure to target occupancy, to pharmacodynamic measures, to clinical outcome). Cases where no such clear chain of events exists are much less convincing and will increase the data requirements regarding robustness and persuasiveness of study results.
Development plan for studies	In very rare disorders, it is important that every patient participating in a study contributes as much information as possible to make a benefit–risk assessment possible. Therefore, the well-planned use of the best available techniques to obtain and analyze information is crucial. This applies throughout the study process from pharmacokinetic and pharmacodynamic modeling to handling and analyses of biopsy material.
Disease models and non-clinical data	Detailed knowledge of the pathophysiology of the disease and the pharmacology of the drug will facilitate the design of efficient clinical studies and will help determine the amount of clinical data required. For rare diseases, preclinical pharmacodynamic studies can be of importance if there exist adequate animal models and may be informative for the design of clinical studies. Such studies may also give important information for dosing and/or route of administration and the investigation of these features in man can be focused.
Choice of endpoints	In other cases, the mode of action of the test treatment may not be well enough known to predict which of several possible outcomes will be affected. In such circumstances, the usual approach of pre-specifying the primary endpoint may be too conservative and more knowledge may be gained from collecting all sensible/possible endpoints and then presenting all the data in the final study report.
Surrogate endpoints	In the context of rare disorders for a given clinical endpoint or validated surrogate endpoint, recruitment of a sufficient number of patients would be difficult or demonstration of this endpoint would take an unreasonable length of time. Then use of other surrogate markers as substitutes for a clinical endpoint may be considered. The term "surrogate endpoint" should only be used for biomarkers, which have been validated. However, selection of a surrogate marker as study endpoint requires it to be reasonably likely – based on epidemiologic, pathophysiologic, or other evidence – to predict benefit. Prediction in itself may not be sufficient to establish efficacy. Considerations should include: • How closely changes in the surrogate endpoint are causally linked to changes in a clinical endpoint or symptom. • How much risk is associated with the therapy • What other therapies (if any) are available for the same condition Demonstrating that a surrogate endpoint adequately reflects the true clinical endpoint is difficult. Epidemiological data and data from patient registers may provide some help.
Ethical considerations	The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results, the latter being the most important. In situations where obtaining controlled evidence on the efficacy and safety of a new treatment is not possible, the regulatory assessment may accept different approaches if they ensure that the patients' interests are protected.
Surrogate endpoints	Surrogate endpoints may be acceptable but need to be fully justified. Their relation to clinical efficacy must be clear so that the balance of risks and benefits can be evaluated.
Patient registers	Patient registers may supply important information on the natural course of disease and may help in the assessment of effectiveness and safety. Furthermore, such registers can be used as a source for historical controls. Registers used in this way should contain high-quality data; GCP inspection might be anticipated.

data that should be available before pediatric trials. A number of malignant diseases may occur principally but not exclusively in children, such as neuroblastoma and medulloblastoma. In contrast, rhabdomyosarcoma is more complex, as evolving biological characterization allows to subdivide soft tissue sarcomas, among which a number of subtypes may occur in adults. A first joint pediatric-adult symposium on drug development was held recently following the scientific debate on the most appropriate separation of adult and pediatric soft tissue sarcomas.

The guideline refers to the similarity of adult and pediatric conditions as a basis for the recommendations as to when pediatric clinical trials should be initiated relative to adult trials. However, it is not clear how to define and judge similarity. Some characteristics to compare pediatric and adult populations are listed in the addendum on pediatric oncology (presented below). The timing of initiation should take into account if there are available and/or authorized treatments for children. Accordingly, in a condition that occurs in children and adults and is life-threatening with no or limited treatments, pediatric trial(s) should start as early as after the "assessment of initial safety data" and "reasonable evidence of potential benefit" from adult studies. Even when a condition affects predominantly or exclusively the pediatric population, as is the case for the majority of pediatric malignant diseases, pediatric trials should commence once initial safety and tolerability data have been obtained, usually in adults. The guideline also states that results of pediatric trials should be part of the initial marketing authorization application.

The guideline recommendations can be implemented according to the European pediatric legislation, Regulation (EC) No 1901/2006, which requires a submission of a development plan as early as after the pharmacokinetic studies in adults, so when adult development is progressing to exploratory therapeutic studies.

The guideline's considerations on extrapolation of efficacy were recently incorporated into a tool box for dynamic decision making and the optimization of pediatric clinical trials (Manolis and Pons 2009). For example, modeling and simulation can help to judge similarity of conditions in adults and children and to investigate factors that influence intervention-response relationships in adults and children. The inclusion in Paediatric Investigation Plans (PIPs) of such techniques was investigated (Manolis et al. 2011). Pharmaceutical companies have extensive experience in advanced biometrical and statistical methods to optimize drug development studies, while experience with such methods for pediatric clinical trials may be limited. Out of 210 agreed PIPs, 47 made reference to modeling and simulation. As an example of such approaches in rare pediatric tumors, the PIP for imatinib requires both the "development and validation of an integrated physiology-based pharmacokinetic (PBPK) or population pharmacokinetics model" and a "measure to extrapolate efficacy to the pediatric population" for the treatment of Kit (CD 117)-positive gastrointestinal stromal tumors and dermatofibrosarcoma protuberans (EMA Web site ref EMEA/759693/2009, P/243/2009). The results of these studies will be the basis for the assessment of imatinib efficacy and safety.

The guideline also includes specific considerations on ethics, safety, and other critical issues in conducting trials in children. More detailed recommendations on ethics of pediatric clinical trials have been published (Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use 2008). These recommendations discuss, in particular, the decreasing ethical need for placebo when evidence in favor of an effective treatment increases. These recommendations apply to pediatric oncology, even though the academic community already makes efforts to account for the patients' best interests and to safeguard patients from low quality studies.

Timely initiation of pediatric trials is also addressed in the following guidance, which is specific of pediatric oncology, covers early pediatric trials, such as dose-finding and initial exploratory therapeutic trials, but not how to demonstrate efficacy in specific pediatric malignant diseases.

2.2.3 Addendum on Pediatric Oncology (CPMP/EWP/569/02)[7]

This addendum is one of several addenda to the note for guidance on evaluation of anticancer medicinal products in man. It came into operation in 2004 and complements the ICH E11 guideline and a general anticancer guideline. It was drafted with the help of experts from the pediatric oncology community, who

[7] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003969.pdf

had earlier on published detailed recommendations on inclusion criteria and how dose-limiting toxicities should be defined (Smith et al. 1998). The addendum requires careful selection of medicines for pediatric trials, based on "extensive testing of new agents in predictive model systems of pediatric tumors at an early stage of preclinical development." This should be carried out by sponsors, irrespective of the target of the development among adult malignancies.

The addendum discusses early dose-finding and therapeutic exploratory clinical trials in children, making recommendations for pediatric-specific aspects of trial designs: For example, the starting dose should be sufficiently high so that pediatric patients can expect some therapeutic effect. Furthermore, intra-patient dose-escalation should be considered when the maximum tolerated dose is not established and toxicity is not a limitation. This may apply to targeted and cytostatic medicines in contrast to cytotoxic medicines, which show maximum tolerated, normalized doses that are almost identical in pediatric and adult dose-finding studies (Lee et al. 2005).

The addendum also addresses how anticancer medicines could be authorized for pediatric patients. A use approved in adults should be extended to the same cancer in children, after consideration of potential differences such as genotypic and phenotypic features, non-clinical activity, human pharmacokinetic and/or pharmacodynamic data on tumor markers, and the available and/or used therapeutic options. The addendum emphasizes the need for a sufficient number of patients studied, with a sufficient number of samples to determine the medicine's pharmacokinetic profile in all the relevant age groups of children.

However, the addendum does not address efficacy trials on rare tumors, although it acknowledges the rarity of the majority of pediatric malignancies.

2.2.4 Summary and Further Guidances

Based on the three guidances presented in this chapter, three major approaches to establish efficacy in the treatment of rare tumors in children can be identified, although not the sole conclusions of the guidances. The guidances encourage to interact with scientists in regulatory authorities on the proposed development plans when alternative approaches to conventional efficacy trials may considered.

- *Extrapolation of efficacy*: Extrapolation of efficacy as outlined in the preceding sections requires availability of adult data from well-designed and -conducted studies in a therapeutic setting that is relevant to the pediatric population. The necessary pediatric trials should focus on pharmacokinetics (PK), preferably using a PK model, and should document the tolerability, safety, and the acceptability of the formulation. Such a trial would normally collect any clinical activity and efficacy indicators, but would not need to be blinded, nor to include an internal control. The trial may be initiated before completion of the adult studies, depending on the strength of the biological rationale and the therapeutic exploratory studies in adults.
- *Bayesian approach based on quantitative assumptions*: This approach would not necessarily require pediatric trials to be powered for testing a superiority hypothesis (e.g., using a log-rank test), but outcome distributions would be combined with prior assumptions (e.g., on progression-free survival or on log-rank test values), and the inference would be the probability for the tested medicine to be beneficial or effective. Although Bayesian designs have rarely been used in submissions for marketing authorization at the European Medicines Agency so far, such approaches are welcome in Paediatric Investigation Plans, or in Scientific advice, as expressed in guidances described in this chapter. This approach has been suggested for rare tumors, on the basis of a theoretical example from pediatric oncology (Tan et al. 2003). In certain situations, a Bayesian approach is close to a prospective meta-analysis as particularly proposed for pediatric oncology (Valsecchi and Masera 1996). Bayesian approaches may be considered for controlled trials, but can also be implemented in single-arm trials (e.g., Thall et al. 1995) with the aim to inform therapeutic confirmatory trials. Bayesian methodology lends itself to a range of practical applications in clinical trials, their design and/or analysis, in early or late phases of development, and for large or small trials.
- *Small self-standing controlled study in relevant population, using multiple endpoints including pharmacodynamic and clinical outcomes*: In the long-standing scientific debate on the ethics of underpowered and thus potentially inconclusive trials, the two preceding sections may be the only justified approaches according to (Halpern et al. 2002). It is however

recognized that small *randomized* trials may be the "only way that any *unbiased* [emphasis added] measurements of effectiveness can be made."[3] In purely pediatric malignant diseases (e.g., neuroblastoma), adult data would not be relevant or might not exist. The small controlled trial would unavoidably be unique as it could not be repeated for confirmation. However, the trial results could be supported by a chain of evidence linking a strong biological rationale (e.g., tumor dependency and knock-out or disease models), xenograft pharmacology studies, dose-response relationships, and available clinical activity/efficacy data, if applicable, from biologically related systems (e.g., overall survival improvement for a cancer histologically unrelated but responsive to similar pathway modulation). The chain of evidence is similar to the pharmacological audit trail proposed for anticancer medicines (Sarker and Workman 2007). To compensate for the small size of the controlled trial, in keeping with general recommendations, the trial could be strengthened by reducing bias, e.g., by blinding, by central review, by meticulous trial conduct, and by inclusion of a broad set of supportive endpoints. With a view to minimizing the number of participants in a clinical trial, it may be possible to assume a large treatment effect, if this is the minimum clinically relevant, realistic effect of a novel medicine worth detecting in a rare tumor with unmet needs. Alternatively, a trial could be discontinued on the basis of futility analyses if the desirable treatment effect cannot be achieved.

2.2.5 Further Guidances

Other European scientific guidelines cover general methodological issues that are relevant to pediatric oncology.

- Methodological Considerations for Using Progression-Free Survival (PFS) as Primary endpoints in confirmatory trials for registration (CHMP/EWP/27994/08)
- Confirmatory studies in Haematological Malignancies (EMEA/CHMP/EWP/520088/08)
- Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design (CHMP/EWP/2459/02)
- Missing data in confirmatory clinical trials (CPMP/EWP/1776/99 Rev. 1)
- Conduct of Pharmacovigilance for medicines used by the pediatric population (EMEA/CHMP/PhVWP/235910/2005-rev.1)
- Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3)
- Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study (CPMP/EWP/2330/99)

The guidances can be accessed at http://www.ema.europa.eu – Regulatory – Human medicines – Scientific guidelines.

2.3 Orphan Medicine Designation

Rare diseases, including the majority of pediatric malignancies, occur so infrequently that the development of medicines for these conditions would be negligible without incentives. The development of a number of incentives was necessary to stimulate the development and placing on the market of medicinal products for the treatment, prevention, and diagnosis of those conditions. These incentives and the criteria to accept the potential use in a defined condition are set up in the different orphan regulations that exist in the world – among others, in the USA since 1983,[8] in Japan since 1993 (Haffner et al. 2008), in Australia since 1997 and in the EU since 2000.[9]

In the European Union, an active substance to treat, prevent, or diagnose a rare condition is designated as an orphan medicinal product according to the following criteria:

- Prevalence of the condition of not more than 5 per 10,000 persons, and either
- Demonstration of insufficient return on investment, or,
- Absence of a satisfactory, authorized method(s) of diagnosis, prevention or treatment, or, if such method exists, a justified assumption that the product will be of significant benefit to those affected by the condition.

[8]Developing Products for Rare Diseases & Conditions. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

[9]Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products. Official Journal of The European Communities. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF

Table 2.2 European marketing authorizations of orphan designated medicines in oncology (February 2011)

Product	Active substance	Condition/indication	Significant benefit shown at time of marketing authorization	Type of initial marketing authorization	Received Scientific Advice (Protocol Assistance)	Pediatric use (indication or dosing recommendation)
Glivec	Imatinib	Chronic myeloid leukemia	Yes	Exceptional circumstances	Yes	Yes
Trisenox	Arsenic trioxide	Acute promyelocytic leukemia	Yes	Exceptional circumstances	No	No
Busilvex	Busulfan	Hematopoietic progenitor cell transplantation	Yes	Normal	Yes	Yes
Onsenal	Celecoxib	Familial adenomatous polyposis	No	Exceptional circumstances	No	No
Litak	Cladribine	Hairy cell leukemia	Yes	Normal	No	No
Lysodren	Mitotane	Adrenal cortical carcinoma	Yes	Normal	No	Yes
Evoltra	Clofarabine	Acute lymphoblastic leukemia	Yes	Exceptional circumstances	No	Yes
Nexavar	Sorafenib	Advanced renal cell carcinoma	Yes	Normal	Yes	No
Sutent	Sunitinib	Gastrointestinal stromal tumor and metastatic renal cell carcinoma	Yes	Conditional	Yes	No
Sprycel	Dasatinib	Acute lymphoblastic leukemia and chronic myeloid leukemia	Yes	Normal	Yes	No
Atriance	Nelarabine	Acute lymphoblastic leukemia	Yes	Exceptional circumstances	No	Yes
Yondelis	Trabectedin	Soft tissue sarcoma	Yes	Exceptional circumstances	No	No
Tasigna	Nilotinib	Chronic myeloid leukemia	Yes	Normal	Yes	No
Torisel	Temsirolimus	Renal cell carcinoma	Yes	Normal	Yes	No
Ceplene	Histamine dihydrochloride	Acute myeloid leukemia	Yes	Exceptional circumstances	No	No
Mepact	Mifamurtide	Osteosarcoma	Yes	Normal	Yes	Yes
Vidaza	Azacitidine	Acute myeloid leukemia and myelodysplastic syndrome	Yes	Normal	No	No
Afinitor	Everolimus	Renal cell carcinoma	Yes	Normal	No	No

Table 2.2 compiles the anticancer medicinal products designated as orphan, and the related regulatory information such as whether significant benefit was maintained at the time of marketing authorization, and which type of marketing authorization had been granted.

2.3.1 Implications for Rare Tumors in Children

The criteria on prevalence for orphan designation refer to the entire population of the European Union, without any reference to subgroups even if the disease manifests itself exclusively in a subgroup. Therefore, conditions affecting children can be designated as orphan when they affect exclusively children or are part of diseases that also occur in adults. In cancer, the situations where the histological and clinical characteristics of the cancer are distinct in children are frequent, making rare cancers in children a natural target for orphan designation. As the prevalence that these orphan conditions must not exceed is based on a calculation with respect to the overall population, if the cancer occurs only in children, the resulting prevalence will be well below the threshold for designation. In any case, since the implementation of the orphan regulation, diseases affecting children have represented a considerable proportion of the total number of designations as shown in Fig. 2.1. This has been particularly notable in 2010 where 18% of the opinions adopted were for conditions affecting children exclusively. On

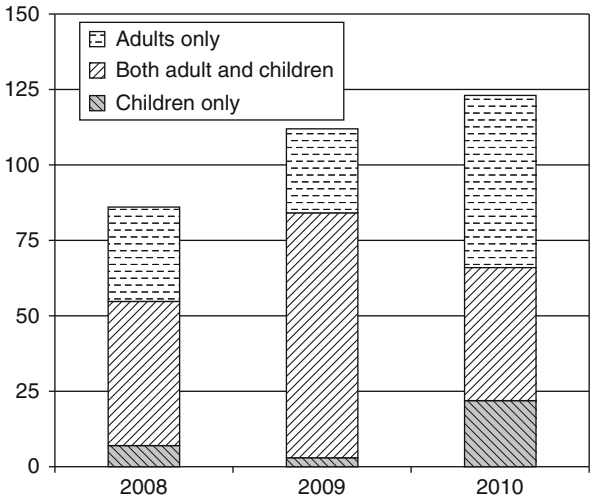

Fig. 2.1 Orphan medicinal product designations in the EU for pediatric and/or adult conditions by year

average the conditions affecting children represented only about 10% over the last 3 years.

Oncology is consistently among designated conditions, the most frequent therapeutic area in respect of numbers of designations (about 30% of the opinions) and at the time of marketing authorization. The same holds true for conditions affecting children, where the relative contribution in oncology is 117 out of the total of 388 opinions (32%) on orphan designation. Among the conditions designated as orphan in pediatric oncology, the most frequent were neuroblastoma, Ewing sarcoma, and medulloblastoma.

2.3.2 Rationale for Development

To obtain orphan designation, the sponsor has to demonstrate that the active substance is of potential therapeutic use in the condition, what is referred to as biological plausibility. Additionally, when other products are authorized for the condition, the sponsor has to demonstrate the potential significant benefit of the medicine. The sponsor is required to provide justifications for these two criteria based on data, although this requirement has to be balanced with the principle that applications for designation can be submitted at any stage during the product development. The fine balance between these two requirements is developed in the "Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation" (EMA/COMP/15893/2009).

Usually, at the time of designation, little or no clinical experience is available. In this situation, the need to justify the biological plausibility of the product must be fulfilled mainly based on in vitro and in vivo non clinical models presented in the application for orphan designation. The model validity and the relevance of the results obtained will have to be discussed for the condition, and where appropriate, references should be made to other products developed for the same condition. If only in vitro evidence is available at the time of the application, the relevance of the findings should be discussed in the context of the proposed condition. The preclinical data provided by these experiments have to be discussed in full, even if preliminary results from first administration to humans are available.

To illustrate this situation, here is a recent example of orphan designation for the treatment of medulloblastoma. The candidate product is a peptide nucleic acid that inhibits MYCN transcription. The transcription of MYCN is associated with the development and progression of the disease, and this is widely accepted in the medical community as a tumor-driving process. Therefore, the medicine's biological plausibility seems acceptable. Moreover, data from experimental models show that the product exerts its action through an antisense mechanism and stops transcription of MYCN. In addition to inhibition of protein expression, the data suggest that the product may induce inhibition of cell growth in MYCN-expressing medulloblastoma cell lines. Data corroborating the plausibility were seen in neuroblastoma. With all these data, the regulatory authorities were able to accept the medical plausibility for orphan designation, keeping in mind that the rationale for the development was justified and that the product deserved further development with the help of incentives from the orphan regulation. This case illustrates the balance between early development and sound and consistent biological data, which sends a strong signal of interest even though there is no guarantee of a successful development.

2.3.3 Significant Benefit

Significant benefit is a criterion for orphan medicine designation that is applied when – in the condition concerned by the application – there are products

authorized for the prevention, treatment, or diagnosis of the condition, whichever is the claimed use of the product. The concept of significant benefit implies an exercise of comparison with authorized treatments or otherwise established methods. As many sponsors apply for orphan designation at an early stage in development when comparative data are often not available, a critical review comparing authorized treatments and the proposed orphan medicinal product, and justifying the assumption of significant benefit should be provided. Importantly, the "review should be based not only on the limitations and risks of the authorized products but also on the benefit expected with the proposed product" according to the recommendation.[10]

There is another point in time when significant benefit is reviewed, which is at the time of marketing authorization. When the development of the product has progressed and allows for a benefit–risk assessment, the significant benefit criterion requires a demonstration and a higher level of evidence than earlier on, at the time of designation.

Significant benefit is defined as "a clinically relevant advantage or a major contribution to patient care" according to Article 3(2) of Regulation (EC) No 847/2000. This broad definition is sufficiently flexible for considering the specific aspects of the pediatric population and the benefit expected for them. In this context, features such as age-adapted formulations, formulations with potentially better compliance, have been specifically considered for the pediatric population, and have been accepted as a valid assumption of significant benefit. Another example is provided by the development of an anticancer drug in a disease where radiation therapy is the main therapeutic option. The medicine could bring significant benefit if the product avoids radiation therapy with its unwanted effects, and this prospect is superior to the potential risks of the medicine. With regards to providing an age-adapted formulation, this has been successfully used as justification for significant benefit when the existing product formulation(s) cannot address the therapeutic needs of the pediatric patients.

At the time of designation, the justification of significant benefit has to be supported by sound scientific arguments and a discussion based on data, either preliminary preclinical or clinical results.

So far, more than 60% of positive opinions adopted on orphan medicine designations were based on the assumption of significant benefit, with the remainder of designations based on absence of satisfactory, authorized method of diagnosis, prevention, or treatment.

2.4 Incentives

In the European Union, a number of incentives, financial and other, have been created for the development of medicines with the aim to improve public health in under-researched areas, and to strengthen the European research area. Indeed, incentives are available throughout the medicine development process (Table 2.3). Some of the incentives apply specifically to pediatric medicines; some incentives are available in European Member States (see "Inventory of rewards and incentives to support medicinal products for pediatric use"[11] published by the European commission based on information from Member States). This section describes incentives available at the European level.

- *Scientific Advice* (*Protocol Assistance*, *in case of an orphan designated medicine*): The European Medicines Agency provides scientific advice on how to optimize the development for a future marketing authorization. This helps applicants to maximize the chances of their marketing authorization application being successful. Scientific advice is free for questions related to pediatric medicine development, and has reduced fees for orphan designated medicines. For micro, small and medium enterprises (SME), there is a substantial fee reduction for scientific advice.
- *Agreement of a Paediatric Investigation Plan* (*PIP*) *or a waiver*: A free procedure for any medicine defining whether a pediatric development is required through a PIP, or is waived. This procedure is mandatory before submission of marketing authorizations. It is provided by the Paediatric Committee (PDCO) of the European Medicines Agency, a scientific body comprising of pediatric experts appointed by member states, of representatives of the EMA's Committee for Medicinal Product for Human Use (CHMP), and of health professionals and patient organization representatives appointed

[10] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf

[11] http://ec.europa.eu/health/files/pediatrics/docs/inventory_on_pediatrics_07-2008_en.pdf

Table 2.3 Support and incentives to the development of medicines for the treatment of rare tumors

Incentive	Provided by	Scope of incentive	Where to start
Fee reductions for European scientific advice and protocol assistance	European Medicines Agency	For any questions on the pediatric development of a medicine Includes regulatory consultation Free Pre-submission meetings and discussion meetings Possibility for parallel advice with US Food and Drug Administration	http://www.ema.europa.eu/ – Regulatory – Scientific advice and protocol assistance
Orphan medicine designation	EMA/European Commission	Protocol assistance, access to central marketing authorization procedure	http://www.ema.europa.eu/ – Regulatory – Orphan designation
SME registration	European Medicines Agency	For micro, small, and medium enterprises (SME) developing medicines, including for example academic spin-offs Regulatory advice throughout all interactions with the European Medicines Agency Special trainings and workshops on scientific topics	http://www.ema.europa.eu/ – Regulatory – SME office
Agreement of Paediatric Investigation Plan (PIP) or Waiver	Paediatric Committee (PDCO) of the European Medicines Agency	Mandatory, Decision on pediatric data required for marketing authorization	http://www.ema.europa.eu/ – Regulatory – Pediatric Medicines
Innovation Task Force (ITF)	European Medicines Agency	Informal information exchange, and scientific guidance early in development process through briefing meetings	http://www.ema.europa.eu/ – Regulatory – Innovation Task Force
Clinical research support	Member States		[a]
Framework programs	European Commission		[b]

[a] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf
[b] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003969.pdf

by the European Commission. Currently, there are several pediatric oncologists in the PDCO, which has a broad coverage of pediatric therapeutic areas. The PDCO agree binding opinions on PIPs or Waivers; in case difficulties are encountered, modifications of PIPs can be requested.

- *When submitting for marketing authorization*: For orphan designated medicinal products, there is direct mandatory access to the centralized marketing authorization procedure to address efficiently European public health needs. New anticancer active substances including those for pediatric use also fall in the mandatory scope of the centralized marketing authorization procedure. New pediatric indications of nationally authorized anticancer medicines have access to the central procedure.
- *When the pediatric medicine development is completed according to a PIP*: Irrespective of whether the data allow authorization for pediatric use, or provide information reflected in the Product Information (PI) recommending that a medicine should not be used in children because of safety or lack of efficacy concerns, a reward may be obtained. This reward may be a 6-month extension of the protection of the medicine's basic patent, or a 2-year extension of market exclusivity (in case of an orphan medicine), or 10-year data exclusivity (in case of a pediatric-only product).
- *When the orphan development is successful*: Orphan medicinal products will benefit from market exclusivity in all EU member states for 10 years after the granting of a marketing authorization. During that period, directly competitive similar products cannot be placed on the market for the same indication. It is not possible either to extend an existing authorization of a similar product for the same orphan indication.

In addition, consortia and sponsors developing orphan or off-patent medicinal products may be eligible for grants from the EU and Member States' programs[6] and initiatives supporting research and development,

including calls for the European Commission framework program.[12]

In any case, academic investigators may be interested by scientific and regulatory exchange about development plans, as described in the following section.

2.5 Opportunities for Scientific and Regulatory Interactions on Pediatric Oncology Developments

A number of opportunities for exchange on scientific questions with the European regulatory network are available at the European Medicines Agency (EMA). The EMA may interact with academic investigators as well as pharmaceutical companies (see also Table 2.3 on available financial incentives for such interactions). The outcomes of such interactions will help to improve or confirm scientifically pediatric trials. The interactions will help to navigate the complex regulatory system and to share responsibility for discussing how to study and develop a medicine.

All interactions are kept confidential by the EMA, but investigators are free to share the outcome (e.g., Scientific advice letter, agreed Paediatric Investigation Plans). During the interaction, EMA will however use its accumulated scientific experience on medicine regulation, trial methodology, successful or failed trials, and related medicinal products. This experience is provided by European experts from various Member States and by the EMA scientific staff, with a view to ensuring that a single European position is developed and communicated.

- *Innovation task force* (*ITF*): The ITF classifies innovative medicinal products, including emerging therapies and technologies, and clarifies the relevant regulatory pathways. A multidisciplinary discussion with the ITF can be requested.
- *Scientific advice* (*SA, called protocol assistance for orphan medicines*): Questions from applicants drive the content of SA. The SA letter (outcome) provides the background considerations and specific answers to requested pharmaceutical quality, non-clinical and clinical questions as well as to significant benefit questions in the case of a protocol assistance. Members of the Paediatric Committee of the EMA are usually involved in pediatric questions of the SA. The SA process aims to complete within 40 days, or 70 days if a discussion meeting is necessary. The SA letter is not binding on applicants. Details on the importance of scientific advice for successful medicine developments have recently been reported (Regnstrom et al. 2010).
- *Paediatric Investigation Plan* (*PIP*): The PIP is a comprehensive view on a medicine development for children, and it includes the studies that are necessary to provide an age-appropriate formulation, non-clinical and clinical trials to conclude on a safe and efficacious pediatric use, including long-term follow-up. A PIP agreed by the EMA Paediatric Committee is binding on applicants, and compliance with the PIP is a requirement for a valid submission of an application for marketing authorization. All agreed PIPs are made public by the EMA on its website, after deletion of commercially confidential information.[13] For example, the design of the agreed studies can be scrutinized by the public.
- *Pediatric oncology task force*: This is an informal group composed of experts from the pediatric oncology scientific communities and of EMA scientists, which meets as needed to discuss general issues related to research into anticancer medicines in the pediatric population. It also serves as a contact point for members of the pediatric oncology community who want to bring issues to attention, such as difficulties attracting early dose-finding and safety trials.
- *Pre-submission meeting with SME office*: After successful registration as a SME, academic consortia could be supported in their interactions with the regulatory system.

Academic investigators can request scientific advice as well as propose a Paediatric Investigation Plan for a medicine. There is no requirement to be a marketing authorization applicant or holder (MAH), or to have an agreement with a MAH. Scientific advice letters and agreed Paediatric Investigation Plans can be then shared and discussed with pharmaceutical companies for the performance of trials.

[12] http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.FP7CallsPage#Health

[13] Oncology: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fpip_search.jsp&murl=menus%2Fmedicines%2Fmedicines.jsp&mid=WC0b01ac058001d129&searchkwByEnter=false&alreadyLoaded=true&keyword=Enter+keywords&searchType=Invented+name&currentCategory=Oncology

Scientific advice is also offered by some national regulatory agencies. This may be of interest to anticipate a clinical trial application.

Any trial with a medicine is of interest to the regulators, because it can provide complementary data on the benefit–risk relationship in an authorized indication, or it can bring data on a potential use of the medicine. New indications may help regulators to address public health needs, which is a major objective of the EMA. Results from such trials and recommendations will then be included in the Product Information (PI) and reflected in the European Public Assessment Report.

For the benefit of all healthcare professionals, special provisions of the Pediatric Regulation (EC) No 1901/2006 were set out to make the PI as informative as possible, such as the submissions and publications of existing trials according to Articles 45 and 46 of the Pediatric Regulation. The recently updated Summary of Product Characteristics (Product Information) guideline[14] requires clear-cut pediatric information if pediatric trials are still awaited, have been waived, or if results allow to recommend the use or not of the medicine.

Obtaining SA may be particularly relevant for rare pediatric tumors, because standard treatment protocols or guidelines may not be available, in contrast to more frequent pediatric malignant diseases.

Other opportunities exist for public exchange of information. The EMA contributes to dialogue at (non-commercial) public scientific meetings, such as ECCO-ESMO, EORTC-AARC-NCI, ASCO, and SIOP meetings. EMA has organized joint meetings with EFPIA and DIA on topics such as adaptive designs, pediatric medicines, and pediatric oncology.

2.6 Collaborative and Organization Aspects of Conducting Trials in Small Populations

In addition to the scientific and methodological aspects, there are other aspects related to the organization and conduct of pediatric oncology trials, which are of importance from a regulatory perspective.

Clinical trials in pediatric oncology share the challenges and requirements of trials in other pediatric therapeutic areas. It may be informative to review the paradigm changes and the methodological progresses in autoimmune diseases and neuromuscular diseases (NDM), for example. The TREAT-NMD network, which involves academic and patient representatives, is organized to collaborate with pharmaceutical companies. It organized with EMA an expert workshop on how to develop novel medicines for the treatment of Duchenne muscular dystrophy (Muntoni 2010).

In malignant diseases that peak in adolescence or young adulthood, conducting safety and efficacy trials open to both pediatric and adult populations should be considered. The pediatric oncology community has made renowned efforts over the last decades to establish pediatric-specific successful treatments. However, for specific research questions, such a combined approach may be reasonable and efficient to simplify and accelerate the setting up of a study and limit the number of trials. When pediatric patients can be included, needs to be carefully considered. If needed, the adult protocol can be opened to pediatric patients through an amendment that takes into account the safety data obtained from the study so far. Such approaches may specially apply to dose-finding and early therapeutic exploratory studies.

The global frequency of pediatric malignant diseases is low. Issues due to differences in standards of care will become more obvious when pharmaceutical companies conduct pediatric oncology trials outside the European and North American regions, e.g., in India and China. For some malignant diseases, e.g., brain tumors, there are even differences among European countries due to different health care systems. Moreover, the "quality control treatment titration studies" as defined by pediatric oncologists for a number of malignant diseases include only some but not all EU member states. Recently, European multinational studies for some pediatric malignant diseases have been set up comparing different treatments in different countries, with the aim to establish an international standard. A PIP aims to generate data that are useful to any children in Europe but may not have the same relevance in every Member State. Pediatric oncology trials in a PIP need to include the best available standard of care despite divergent scientific views and availabilities of treatment options, e.g., high-dose therapy.

When discussing Paediatric Investigation Plans with pharmaceutical companies, the Paediatric Committee would like to see academic communities involved, in

[14] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

the treatment, setting up of registers, or clinical research, or as pediatric networks.

Before the start of trials with novel medicines or in a novel indication, agreements between academia and pharmaceutical companies are encouraged. Such trials are relevant to the refinement and understanding of the benefit–risk relationship of the medicine. Public access to the resulting information through regulatory assessment can be construed as an ethical duty, even more when investigator-initiated trials have received public funding. The consent form and other templates[15] of the US National Cancer Institute for sponsored trials in pediatric oncology explicitly mention that data will be shared with regulatory authorities, and templates for contracts and SOPs have been made freely available by platforms such as the TMF.[16]

2.7 Lack of Efficacy

Trial results are usually analyzed for any indicators of efficacy, but analyses should be open for the possibility that the data may indicate a lack of efficacy. In a rare condition, the treating physician may rely on low levels of evidence in favor of the efficacy of a treatment. However, if the treatment is ineffective, patients suffer from a loss of chance, and can be harmed, as toxicity will still occur, and increased by higher doses given when the activity (response) is unsatisfactory. Convincing evidence of lack of efficacy could come from large controlled studies, which are not available in rare tumors. For example, we propose that the following is considered in the case of rare tumors:

- Formulate and pre-specify assumptions on minimum treatment effect that is clinically relevant and desirable, or expected to change medical practice. The definition should be achieved by consensus of the community whose members will later take decisions for their patients.
- Ensure that clinical results are published and interpretations are clearly communicated and implemented in medical practice, e.g., in therapeutic guidelines. Conclusions should also specify whether the same medicine may be further tested, and if another medicine would be tested in subsequent trials.
- Absence of evidence of efficacy is not evidence of absence of efficacy for a medicine. A careful analysis should look into whether non-positive study results may be related to the design and conduct of a study, and if signs of activity of the medicine could be picked up. Any further use of such a medicine should take place in a controlled environment, that is, in a clinical trial. More evidence (positive or negative) would be built up and patients would be protected.

There are few examples where marketing authorizations granted conditionally have been revoked based on lack of efficacy shown in further studies (Richey et al. 2009). Regulatory agencies have seen negative efficacy studies of authorized anticancer medicines in a new therapeutic setting of the same malignant disease. Data from "negative" pediatric trials are included in the European Public Assessment Reports, even when the pediatric malignant diseases studied were not related to the authorized adult indications (e.g., Torisel (temsirolimus)).

2.8 Conclusions and Outlook

This chapter summarized some regulatory aspects relevant to pediatric trials, the opportunities to obtain scientific-regulatory advice, as well as incentives and support available to academic researchers, be they academic investigators or investigators in pharmaceutical company–sponsored projects on the development of anticancer medicines.

The European Medicines Agency is building up experience in oncology (Pignatti et al. 2002), including pediatric oncology, although too few new anticancer medicines are available for children, in particular to treat rare tumors. As expressed in the European Medicines Agency Road Map on its contribution to science, medicines, and health,[17] the paradigms for authorization, information, and surveillance of medicines are evolving fast, and greater uncertainty on a medicine may be a trade-off for earlier availability (Eichler et al. 2008).

However, the development of new medicines requires the generation of as much as possible data, so to quantify and characterize what is known of the

[15] http://www.cancer.gov/clinicaltrials/education/simplification-of-informed-consent-docs/page3

[16] http://www.tmf-ev.de/EnglishSite/ProductsServices.aspx

[17] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000292.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac05800293a4

medicine's efficacy and safety and to reduce uncertainty as much as possible.

In keeping with this principle, trials in pediatric oncology cannot be seen in isolation, even when conducted by individual investigators, but as public contributions to build up evidence; trials should be designed with support from scientists at regulatory agencies. All such contributions, positive or negative, should be made available to the public and to agencies, for evaluation and eventually inclusion in Product Information. This would honor and respect each child patient participating in clinical research. This is an ethical imperative to make new medicines available to children with rare tumors.

2.9 Suggested Further Reading and Resources

- Introduction to the European regulatory system: User guide for micro, small and medium-sized enterprises (SMEs) on the administrative and procedural aspects of the provisions, laid down in regulation (EC) No 726/2004. This guide is of particular relevance to SMEs, but provides a useful overview of the system. http://www.ema.europa.eu – Regulatory – Human Medicines – SME office – Guidance
- Scientific guidance of the European Medicines Agency, http://www.ema.europa.eu – Regulatory – Human medicines – Scientific guidelines – Clinical efficacy and safety – Antineoplastic and immunomodulating agents
- Recent scientific-regulatory presentations by the European Medicines Agency and its network, http://www.ema.europa.eu – Document library – Filter by document type: Presentations
- Scientific training resources on Rare Diseases Europe (Eurordis), http://www.eurordis.org/training-resources
- Reports on the European Medicines Agency's workshops with pediatric experts, http://www.ema.europa.eu – Regulatory – Human medicines – Paediatric medicine – Related information – Workshops
- Reports on scientific-regulatory workshops of the EMA SME office, http://www.ema.europa.eu – Regulatory – Human Medicines – SME office – Workshops
- Scientific evaluation guidance in EMA/PDCO summary reports on Paediatric Investigation Plans, http://www.ema.europa.eu/docs/en_GB/document_library/Templates_and_Form/2009/09/WC500003740.doc
- Medicinal products for human use authorized by the European Commission, http://ec.europa.eu/health/human-use/index_en.htm: European community medicine registers, News on pharmaceuticals and updates on Medicines for children
- EU Legislation (Eudralex) http://ec.europa.eu/health/documents/eudralex/index_en.htm

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References

Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use (2008) Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf (accessed 18 September 2011).

Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A (2008) Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 7(10):818–826. doi:10.1038/nrd2664

Haffner ME, Torrent-Farnell J, Maher PD (2008) Does orphan drug legislation really answer the needs of patients? Lancet 371(9629):2041–2044. doi:10.1016/S0140-6736(08)60873-9

Halpern SD, Karlawish JHT, Berlin JA (2002) The continuing unethical conduct of underpowered clinical trials. JAMA 288(3):358–362

Koschmann C, Thomson B, Hawkins DS (2010) No evidence of a trial effect in newly diagnosed pediatric acute lymphoblastic leukemia. Arch Pediatr Adolesc Med 164(3):214–217. doi:10.1001/archpediatrics.2009.282

Lee DP, Skolnik JM, Adamson PC (2005) Pediatric phase I trials in oncology: an analysis of study conduct efficiency. J Clin Oncol 23(33):8431–8441. doi:10.1200/JCO.2005.02.1568

Manolis E, Pons G (2009) Proposals for model based paediatric medicinal development within the current EU regulatory framework. Br J Clin Pharmacol 68(4):493–501. doi:10.1111/j.1365-2125.2009.03484.x

Manolis E, Eldirdiry Osman T, Herold R, Koenig F, Tomasi P, Vamvakas S, Saint RA (2011) Role of modeling and simulation in pediatric investigation plans. Paediatr Anaesth. doi:10.1111/j.1460-9592.2011.03523.x, http://www.ncbi.nlm.nih.gov/pubmed/21244569

Muntoni F (2010) The development of antisense oligonucleotide therapies for Duchenne muscular dystrophy: report on a TREAT-NMD workshop hosted by the European Medicines Agency (EMA), on September 25th 2009. Neuromuscul Disord 20(5):355–362. doi:10.1016/j.nmd.2010.03.005

Peppercorn JM, Weeks JC, Cook EF, Joffe S (2004) Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet 363(9405):263–270. doi:10.1016/S0140-6736(03)15383-4

Pignatti F, Aronsson B, Vamvakas S, Wade G, Papadouli I, Papaluca M, Moulon I, Le Courtois P (2002) Clinical trials for registration in the European Union: the EMEA 5-year experience in oncology. Crit Rev Oncol Hematol 42(2): 123–135

Raphaël M, le Deley M, Vassal G, Paoletti X (2010) Operating characteristics of two independent sample design in phase I trials in paediatric oncology. Eur J Cancer. doi:10.1016/j.ejca.2010.01.024, http://www.ncbi.nlm.nih.gov/pubmed/20176476

Ratain M (2010) Bar the windows but open the door to randomization. J Clin Oncol 28(19):3104–3106. doi:10.1200/JCO.2010.29.3787

Regnstrom J, König F, Aronsson B, Reimer T, Svendsen C, Tsigkos S, Flamion B, Eichler HG, Vamvakas S (2010) Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur J Clin Pharmacol 66(1):39–48. doi:10.1007/s00228-009-0756-y

Richey EA, Lyons A, Nebeker JR, Shankaran V, McKoy JM, Ha Luu T, Nonzee N et al (2009) Accelerated approval of cancer drugs: improved access to therapeutic breakthroughs or early release of unsafe and ineffective drugs? J Clin Oncol 27(26):4398–4405. doi:10.1200/JCO.2008.21.1961

Sarker D, Workman P (2007) Pharmacodynamic biomarkers for molecular cancer therapeutics. Adv Cancer Res 96:213–268. doi:S0065-230X(06)96008-4

Smith M, Bernstein M, Bleyer WA, Borsi JD, Ho P, Lewis IJ, Pearson A et al (1998) Conduct of phase I trials in children with cancer. J Clin Oncol 16(3):966–978

Tan SB, Dear KBG, Bruzzi P, Machin D (2003) Strategy for randomised clinical trials in rare cancers. BMJ 327(7405):47–49. doi:10.1136/bmj.327.7405.47

Thall PF, Simon RM, Estey EH (1995) Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med 14(4):357–379

Valsecchi MG, Masera G (1996) A new challenge in clinical research in childhood ALL: the prospective meta-analysis strategy for intergroup collaboration. Ann Oncol 7(10): 1005–1008

Rare Tumors: Pathology and Biology Perspectives

3

Bahig Shehata and Sarah Shulman

Contents

3.1 Introduction

The study of pediatric rare tumors is complicated at many levels. Accurate pathologic identification is essential, yet pediatric expertise is limited. For success, various collaborations are crucial. First, surgeons and pathologists must coordinate their efforts prior to surgery to ensure that sufficient material is obtained and that material is handled appropriately. Second, pathologists must be willing to consult others who may have more expertise. Two examples are a central review team (as developed in pediatric oncology groups) or pathologists with specific skills in adult tumors. Biological studies are also crucial to success in the study of rare pediatric tumors. As the whole-genome project moves forward, clinicians and investigators must be prepared to apply new information and molecular analysis methods to further understand the etiopathogenesis of those tumors. Two successful examples of molecular characterization in pediatrics: the pleurapulmonary blastoma family of diseases (Hill et al. 2009) and midline carcinoma with NUTT gene rearrangement (French et al. 2004). Further progress will be hampered if we do not establish a clear strategy to collect and store precious rare tumor material for future study. In addition, biological data must be fully integrated with data from clinical registries to fully enhance studies on rare pediatric tumors.

3.2 Pathological Diagnosis: Problems of Classification and Impact of Central Pathologic Review

In the last four decades, the 5-year survival rate for childhood cancer patients has improved from 58% to over 80% (Smith et al. 2010). This improvement can

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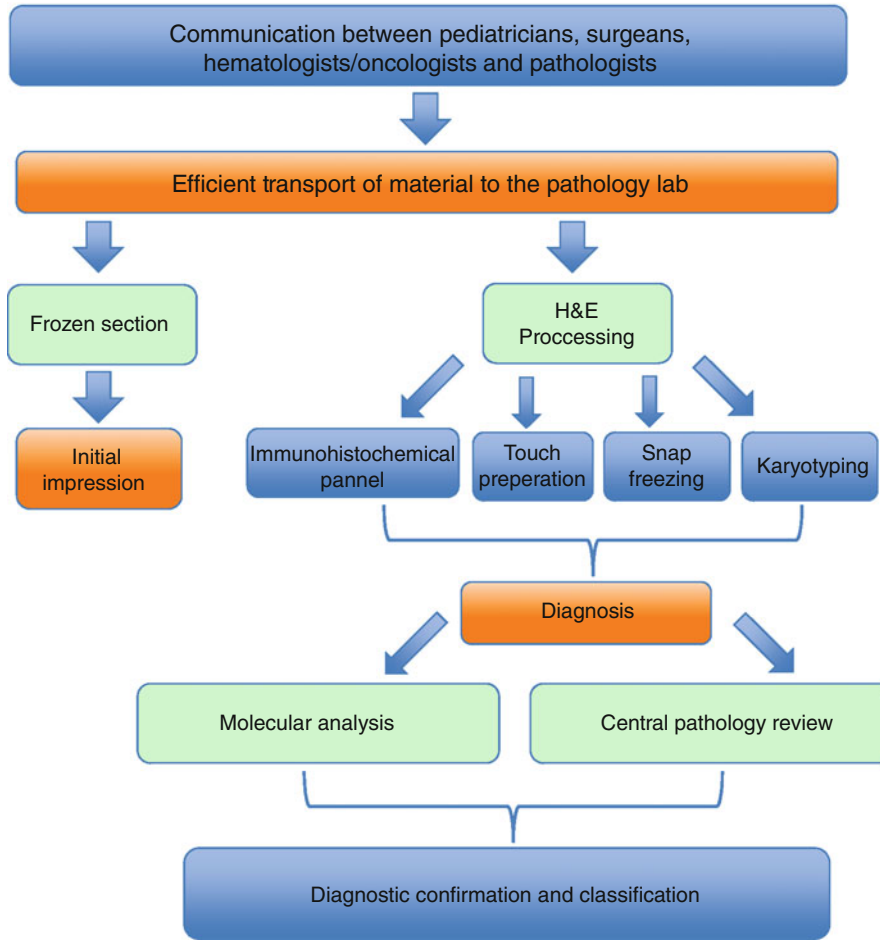

Fig. 3.1 Communication leads to expedited and improved diagnosis

be attributed to the dedicated work of the many national and international pediatric oncology treatment groups and the impact of central pathology review and the classification and subclassification of childhood tumors using advanced immunohistochemical and molecular genetic techniques. Despite the human genome revolution of 2000, this upward trend has reached a plateau. One obstacle to improving the survival rates of childhood cancer patients is imprecise tumor classification based only on morphology. The traditional classification and diagnostic methods of hematoxylin and eosin (H&E), immunohistochemistry, conventional karyotyping, and fluorescence in situ hybridization (FISH) have almost reached their maximum potential. Clinicians and researchers have yet to fully utilize copy number variation analysis, single nucleotide polymorphism (SNP) arrays, methylation analysis, singling pathway analysis, and whole-genome sequencing to create distinct classifications for childhood tumors based on their molecular/genetic basis. The ultimate key to increased survival rate and the future of tumor classification and diagnosis lays in understanding the molecular/genetic basis of childhood tumors (Tschoep et al. 2007).

Departmental cooperation is the first step in ensuring the correct classification of rare childhood tumors. The process is described in Fig. 3.1. First, the referring pediatrician, oncologist, surgeon, and pediatric pathologist must be involved in all aspects of the decision process. This will assure that the appropriate procedures are performed and that tissue is received in a fresh and sterile state (Demeure et al. 2010). Before a lesion is biopsied or a tumor is removed, clinical information about the patient is generally reviewed.

Although this data can help formulate a preoperative clinical differential diagnosis, it is not uncommon for the pathologist to be faced with an unexpected type of tumor. Conflicting preoperative data and pathological findings can ultimately create difficulties in reaching a final diagnosis. The challenge of making a quick and confident diagnosis becomes greater if strict handling of tumor tissue is not followed. Receipt of high-quality tumor specimens will not only aid in the classification and diagnosis of the tumor but it will allow the patient to be enrolled in the appropriate cooperative study (Oosterhuis et al. 2003).

It is extremely imperative that fresh tumor tissue is sent to the pathology department from the operating room as quickly as possible. Upon specimen arrival, initial examination of a preliminary frozen section helps to identify the nature of the tumor and to assure that the material saved in the biorepository is of the highest quality. Touch preparations are then made for future FISH analysis, tissue is snap frozen for permanent banking, and more tissue is sent for karyotyping. In cases where a hematologic malignancy is suspected, additional tissue will be sent to the flowlab. Any delay in tissue banking increases the chance for RNA and DNA degradation which will negatively impact its ability to be used in further research. Therefore, an open line of communication between surgeons and pathologists is fundamentally important to assure expedition of this process and to prevent any unnecessary compromise to the quality of the tumor sample (Oosterhuis et al. 2003).

After tissue is processed and H&E slides are examined, a panel of immunohistochemical stains is ordered to help support the original impression about the nature of the tumor. Karyotyping is also requested to identify any obvious translocations/deletions that might narrow the differential diagnosis. It is not uncommon in cases of rare tumors, even after following theses strict steps, that a final diagnosis cannot be rendered. Microscopically, many childhood tumors look alike. Using these traditional techniques, it is difficult to predict with certainty the histogenesis, phenotype, metastatic potential, genomic alteration, therapeutic response, and outcome of the majority of childhood tumors. In the instance of rare tumors, based on morphology alone, a vague diagnosis such as "sarcoma NOS" and "neoplasm with unknown malignant potential" are often rendered.

Immunohistochemical panels are often also inconclusive. With the implementation of every new immunohistochemical marker, clinicians believed that it would help differentiate between distinct tumor groups. Unfortunately, many immunohistochemical markers have proven to be tumor sensitive but not tumor specific. For example, all specimens labeled as rhabdomyosarcomas that were sent to the central pathology review had the same immunohistochemical panel. Preliminary studies of the rhabdomyosarcoma registry using comparative genomic hybridization (CGH) have shown that the genetic makeup of approximately 15–20% of specimens is not compatible with that of conventional rhabdomyosarcoma. Although the difference in tumor type is now clear, those patients are still enrolled in rhabdomyosarcoma treatment protocols (Morotti et al. 2006). The discovery of the diagnostic inaccuracy in a relatively straightforward case, such as rhabdomyosarcoma, only further elucidates the diagnostic and classification issues with difficulty and rare tumors.

A separate example illustrating the failures of conventional diagnostic tools pertains to a newborn who was clinically diagnosed with stage IV S-neuroblastoma. The histology showed an undifferentiated neoplasm composed of large epitheliod cells, which was not supportive of the clinical diagnosis (Fig. 3.2). Additionally, a large panel of immunohistochemical stains was nonconclusive. After a week, karyotyping results showed at (15:19), and a diagnosis of NUT midline carcinoma was finally reached (French et al. 2004). This case illustrated the inadequacies of histology and immunohistochemical stains while highlighting the need for molecular/genetic analysis. While conventional karyotyping proved to be useful in this instance, it is clear that other undifferentiated tumors can be defined by further molecular/genetic techniques when conventional karyotyping fails (Shehata et al. 2010).

Although conventional karyotyping is helpful in identifying specific translocations for certain tumors, this method misses many tumor genome mutations such as loss of heterozygosity (LOH) events and microdeletions. These mutations can be detected using copy number variation technology or whole-genome mapping. For example, tuberous sclerosis is characterized by the mutation of the *TSC1* or *TSC2* genes, and it is associated with rare renal tumor manifestations (Henske 2005). In several instances, mutations in these genes are not identified by conventional karyotyping. However, they can be seen in SNP copy number array analysis. In children with renal tumors, a quick and

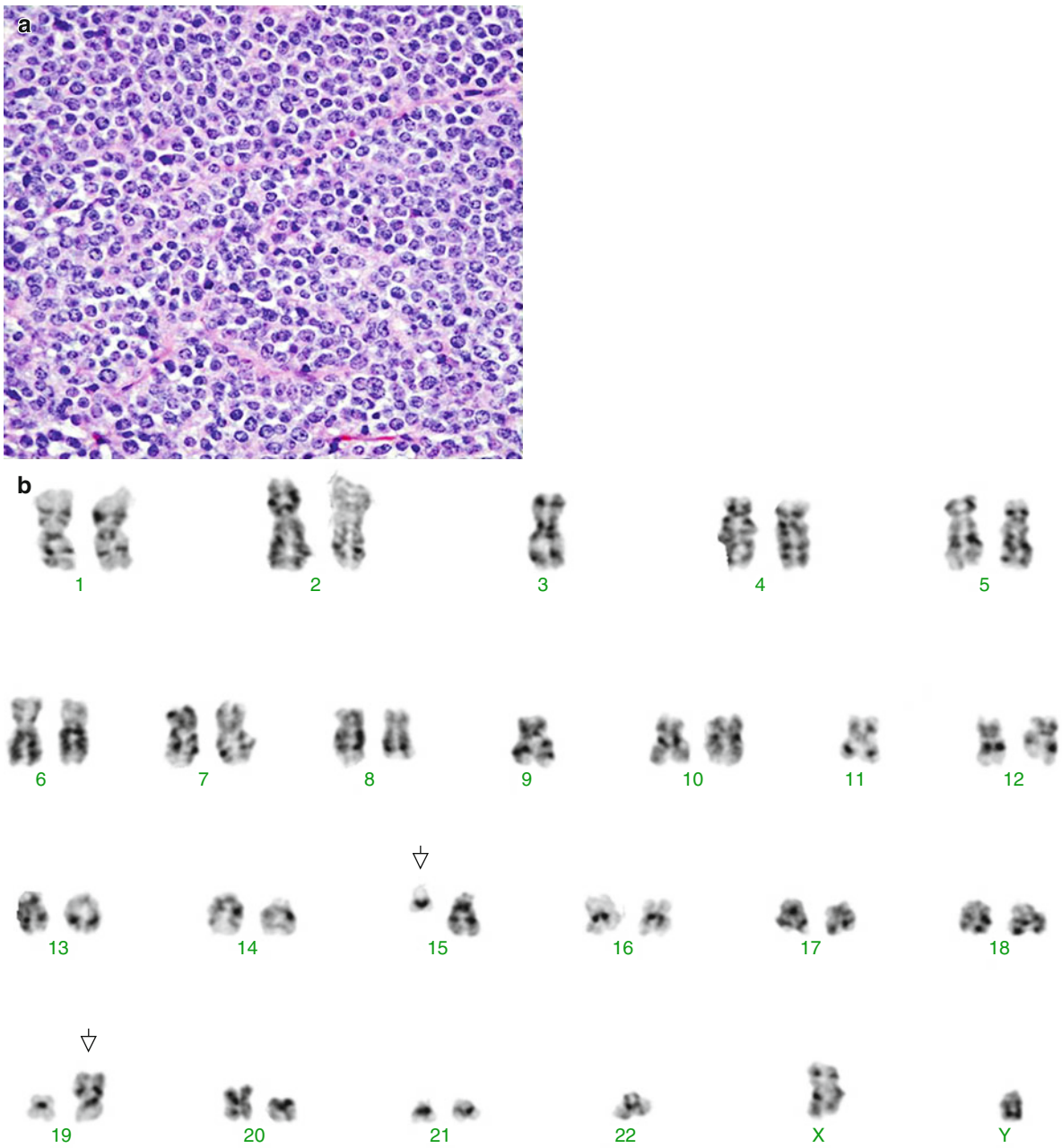

Fig. 3.2 (**a**) Sheets of poorly differentiated epitheliod cells. (**b**) Translocation of chromosome 15 and 19 (NUTT gene rearrangement)

accurate diagnosis of tuberous sclerosis using this technique will ultimately help in the diagnosis of rare associated renal tumors such as angiomyolipoma.

Classification can be further accomplished through the comparative analysis of tumor tissue and non-tumor tissue from each patient. Comparative genomic hybridization cannot only explain why a patient has a specific tumor but it can also provide important data to the survivorship program to have a road map for the follow-up surveillance of this patient. Should the child have a second malignancy, this data can help to explain if the child was susceptible to have the second

malignancy or if it was induced by the treatment regimen. Therefore, collection of tumor and non-tumor tissue is very valuable for the prognosis and follow-up of childhood cancer patients (Weiss et al. 2003).

Overall, in depth, molecular/genetic analysis will allow for greater elucidation about the genetic alterations, present in tumors, which may lead to the development of those particular tumors. Subclassifications of certain tumor types may be more readily formed using these newly developed techniques. This will allow researchers and clinicians to develop more specific treatment protocols based on the prognosis of patients with each subclassification. Therefore, the future of tumor classification and diagnosis, as well as treatment protocol development, lies in molecular/genetic sequencing. However, even the molecular diagnosis of rare childhood tumors remains problematic. The definition of characteristic genetic profiles may be limited by the paucity of cases. While the diagnostic and prognostic impact of chromosomal translocations has been well defined in childhood leukemia, it is almost impossible to perform comparable prospective research in rare solid tumors. If these patients are not registered on therapeutic clinical trials, collection of biological material is unlikely. If a new and recurrent genetic aberration is reported in a rare tumor, the frequency as well as the diagnostic and prognostic impact of the aberration will be elusive for a period of time.

One of the cornerstones of the major success in the treatment of childhood cancers is the impact of central pathology reviewers. In the United States, several groups are charged with reviewing specific tumors including, Wilm's tumor, rhabdomyosarcoma, neuroblastoma, etc. Their ultimate goal is to verify original diagnoses and to assure the collection of biological material for the central biorepositories of the Children's Oncology Group. After reviewing each case, the central pathology reviewers provide feedback to the referring institutions by agreeing, correcting, clarifying, or adding additional information. This collaborative effort is educational and plays a significant role in the management of patients (Teot et al. 2007). In Germany, the vast majority of tumor samples, collected from patients enrolled on therapeutic trials, undergo review at the German Childhood Tumor Registry in Kiel. Brain tumors are reviewed at the German Brain Tumor Registry in Bonn. Pathologic review is mandatory for most protocols, and reference pathologic evaluation is covered financially. Central review ensures uniform diagnosis and classification, but also fosters molecular genetic research on childhood tumors.

Central pathology reviewers are privileged to see a spectrum of cases, giving them the ability to observe specific prognostic factors, which helps in the implementation of standard protocols. Central pathology reviewers also compare the outcomes of specific protocols during the semiannual meetings for COG. This process leads to the initiation of additional studies and the enhancement of existing protocols (Teot et al. 2007). Central review has a more significant impact in the diagnosis and classification of ambiguous rare tumors in comparison to more common childhood tumors. In recent years, the collection of frozen material has been used to bolster the efforts of the molecular analysis of such tumors. The future molecular analysis of rare tumors by the central pathologic review will further help classify these tumors so that individualized treatment protocols can be created. Ultimately, the wealth of the material that they receive will strengthen the classification and reclassification of rare childhood tumors.

Rare tumors have not been well studied. It is difficult to collect sufficient numbers of any particular tumor for biologic studies. Slowly, international collaborations have allowed access to more biological material for some rare pediatric cancers. Rare childhood tumors are not only difficult to classify, but they are also difficult to diagnosis and manage. A more in depth classification of rare childhood tumors will allow for the development of tailored treatment protocols which will help to minimize the rate of relapse and the development of treatment-related malignancies. There has been significant collaboration in the classification of some pediatric cancers, such as rhabdomyosarcoma and neuroblastoma. More collaboration is needed. Ultimately, through the continued work of the central pathology reviewers and the use of molecular/genetic analysis, we can begin to better understand rare childhood tumors and again increase the overall childhood cancer survival rate.

3.3 Tissue Banking

Tremendous improvement in the treatment of childhood cancer and survival of pediatric cancer patients has occurred over the last 30 years as the result of the

use of pediatric cooperative group clinical trials. It is clear that additional significant progress, especially in the treatment of rare tumors, will require an improved and more comprehensive understanding of the molecular genetic basis of pediatric malignancies as well as the specific alterations which underlie resistance to current therapies (Oosterhuis et al. 2003). The National Cancer Institute (NCI) Best Practices for Biospecimen Resources (June 2007) states that the lack of standardized, high-quality biospecimens is widely recognized as a significant roadblock to cancer research. To remove this obstacle, tumor tissue biorepositories need to be created immediately (Demeure et al. 2010).

Tumor banking, while considered a fairly new concept, is still widely known as the most effective method for saving, storing, and delivering high-quality biospecimens for research (Demeure et al. 2010). The current shift from histological means to molecular means in cancer diagnosis, treatment, and research clearly necessitates the development of high-quality tumor banks (Oosterhuis et al. 2003).

Little is known about the etiopathogenesis of childhood tumors. In particular, the infrequent occurrence of rare childhood tumors hinders our ability to garner statistically valid data concerning this subset of tumors. The main goal of pediatric tumor banks is to improve the diagnostic accuracy of pediatric tumors and advance the fundamental knowledge in tumor biology through the preservation of such rare specimens (Oosterhuis et al. 2003). This information will impact the survival rate and long-term quality of life for pediatric cancer patients by providing treating clinicians with more precise diagnoses for targeted therapies and research scientists with high-quality biospecimens (Demeure et al. 2010).

Molecular analysis will help identify candidate genes that denote diagnosis, prognosis, and potential targets for each specific childhood tumor (Tschoep et al. 2007). This will lead to a more accurate pathological diagnosis, and therefore, more precise, targeted molecular therapies (pharmacogenetics) will be made available that can be delivered to tumor cells (Tschoep et al. 2007). These specialized treatments will improve survival and minimize short-term and long-term side effects (Nair 2010). This would represent a huge turning point in pediatric cancer care since the current chemotherapy and radiation therapy treatment methods have many pathological side effects and can impact children's growth and intelligence. This in itself will provide for better survivorship, long-term health, and reduction in second malignancies.

The quality of the results produced by molecular analysis depends on the quality of the tissue samples that are used (Oosterhuis et al. 2003). To ensure a national (or international) standard of tumor biorepositories and the maximization of results, certain tumor bank criteria should be met: the collection of high-quality tumor samples for molecular analysis, the storage of fibroblast cultures and blood to allow for the comparison between genomics of tumor and non-tumor tissue, the standardization of collection and storage to assure high-quality specimens, the continued implementation of standardized protocols based on national standards, and the implementation of statewide educational seminars to strengthen scientific understanding and improve tissue acquisition (Holland et al. 2003; Demeure et al. 2010). A practical approach is detained in Fig. 3.3. The collection of fibroblast cultures is especially important as it allows for the identification of mutations in somatic cells that may explain the current malignancy or any future second malignancies. Although tumor tissue is routinely sent to central suppositories under Children's Oncology Group protocols, the creation of a statewide pediatric tumor banks will give local cancer researchers easy access to substantial numbers of specimens in order to perform their research. Comparable central repositories have also been built in other countries. One example is the BioCase project. Fresh tissue is collected from patients with embryonal tumors (e.g., neuroblastoma) enrolled on prospective clinical trials (Ernestus et al. 2006). The days of attempting to locate specimens piecemeal can be put to bed, and the delays currently experienced for critical research can be made null and void.

According to the National Cancer Institute, there are 11 million cancer survivors alive in the United States. At least, 270,000 survivors were originally diagnosed at age <21 years. Today, approximately 80% of children affected by cancer are alive 5 years after diagnosis (Smith et al. 2010). Collaboration between Pathology Departments, Hematology–Oncology Departments, Surgery Departments, and Clinical Research is crucial for the successful establishment of high-quality tumor banks (Demeure et al. 2010). The implementation of tumor banks around the world can help further our knowledge about rare tumors, increase the number of childhood cancer survivors, and decrease the short-term and long-term side effects of cancer treatment through

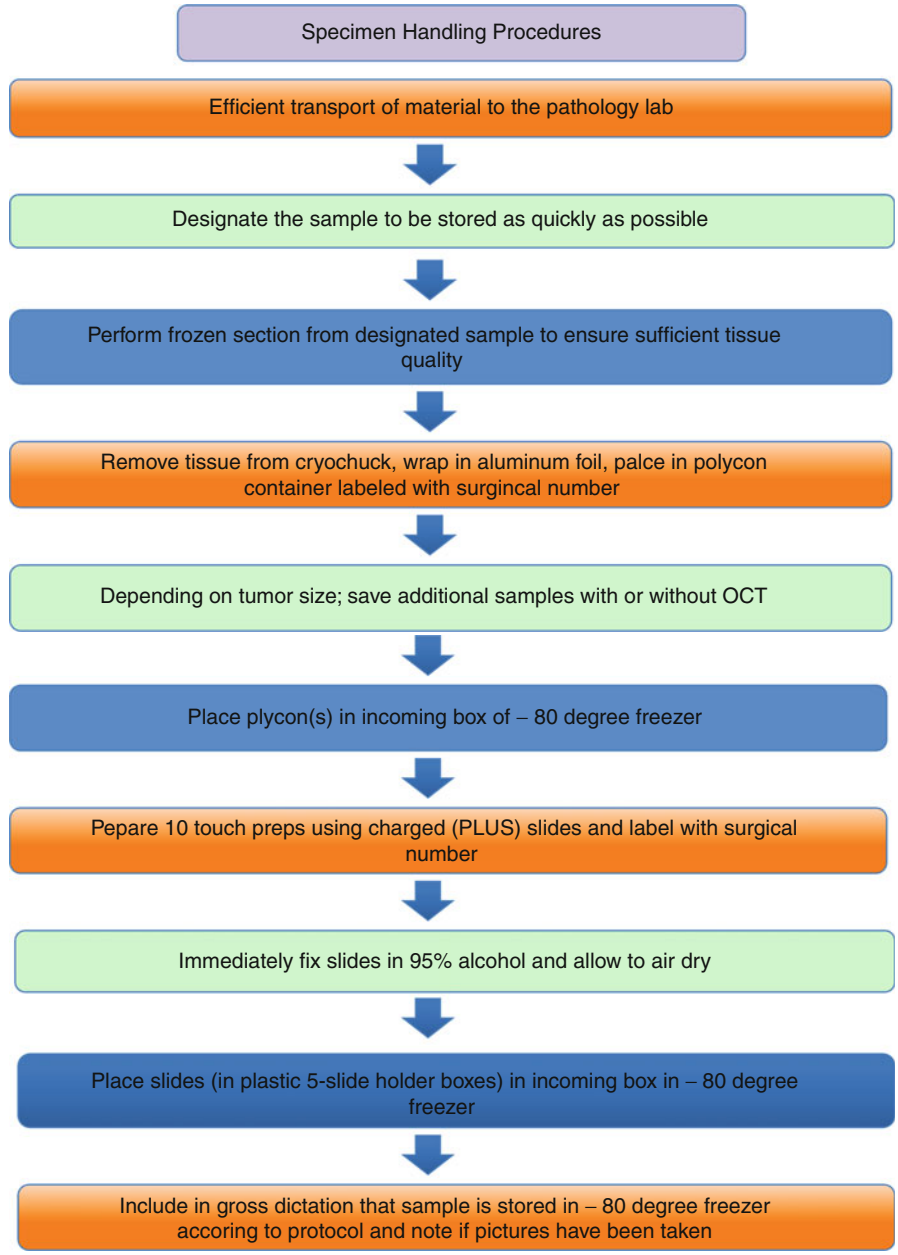

Fig. 3.3 Handling of material for diagnostic studies and tumor banking

the identification of candidate genes and the development of target therapies.

However, several obstacles must be overcome. In particular, complex ethical and legislative issues have urgency. The distribution of tissue samples to "foreign" laboratories may be sanctioned if no specific consent has been previously obtained. It would be preferred that future consent for tissue includes the opportunity that precious material might be shared with international investigators. However, shared samples must be anonymous. Corresponding clinical data must be held at local institution or cooperative group that is authorized, under consent process, to review clinical data. If these issues can be overcome, international cooperation may stimulate molecular genetic research on rare childhood cancers and intensify the development of clinical and

scientific networks, which are essential for the treatment of these patients. Molecular analysis and the characterization of the cancer genome must be performed to reach the ultimate goal of a complete cure for cancer. Tumor banking is the tool necessary to reach this goal.

References

Demeure MJ, Sielaff T et al (2010) Multi-institutional tumor banking: lessons learned from a pancreatic cancer biospecimen repository. Pancreas 39(7):949–954

Ernestus K, Pietsch T et al (2006) Structure, use, and risks of biomaterial repositories of embryonal tumors. Klin Padiatr 218(3):132–138

French CA, Kutok JL et al (2004) Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol 22(20):4135–4139

Henske EP (2005) Tuberous sclerosis and the kidney: from mesenchyme to epithelium, and beyond. Pediatr Nephrol 20(7):854–857

Hill DA, Ivanovich J et al (2009) DICER1 mutations in familial pleuropulmonary blastoma. Science 325(5943):965

Holland NT, Smith MT et al (2003) Biological sample collection and processing for molecular epidemiological studies. Mutat Res 543(3):217–234

Morotti RA, Nicol KK et al (2006) An immunohistochemical algorithm to facilitate diagnosis and subtyping of rhabdomyosarcoma: the Children's Oncology Group experience. Am J Surg Pathol 30(8):962–968

Nair SR (2010) Personalized medicine: striding from genes to medicines. Perspect Clin Res 1(4):146–150

Oosterhuis JW, Coebergh JW et al (2003) Tumour banks: well-guarded treasures in the interest of patients. Nat Rev Cancer 3(1):73–77

Shehata BM, Steelman CK et al (2010) NUT midline carcinoma in a newborn with multiorgan disseminated tumor and a 2-year-old with a pancreatic/hepatic primary. Pediatr Dev Pathol 13(6):481–485

Smith MA, Seibel NL et al (2010) Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 28(15):2625–2634

Teot LA, Sposto R et al (2007) The problems and promise of central pathology review: development of a standardized procedure for the Children's Oncology Group. Pediatr Dev Pathol 10(3):199–207

Tschoep K, Kohlmann A et al (2007) Gene expression profiling in sarcomas. Crit Rev Oncol Hematol 63(2):111–124

Weiss MM, Kuipers EJ et al (2003) Comparative genomic hybridisation as a supportive tool in diagnostic pathology. J Clin Pathol 56(7):522–527

Part II

Epidemiology and Etiology of Rare Cancers

Epidemiology

4

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Contents

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4.1 Introduction

A rare disease affects a small percentage of the population. There had been several efforts to define rare diseases, but so far no single cutoff point has been agreed on for which a disease is considered rare, and no single definition for rare diseases exists. Some characteristics of rare diseases have let to the expression "orphan disease" and influenced the definition of rare diseases: rare diseases are often of genetic origin, thus chronic, and symptoms appear early in life; they might be inadequately diagnosed and treated. The interest of the pharmaceutical industry to develop new drugs is generally low as the rarity of the disease leads to little financial incentive. Also, a rare disease might be rare in a particular part of the world or in a specific group of people. The United States Rare Disease Act of 2002 defines a rare disease as "any disease or condition that affects less than 200,000 persons in the United States," which is a prevalence of 1 in 1,500 people or less (National Institutes of Health (2010)). The European Commission on Public Health includes more criteria but prevalence by defining rare diseases as "life threatening or chronically debilitating diseases with a low prevalence (1 in 2,000) and a high level of complexity" (European Parliament and the Council of Europe, http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf). According to this definition, it is estimated that around 6,000 different rare diseases exist in Europe, and 6–8% of the population is affected by a rare disease (European Organization for Rare Diseases, EURORDIS, http://www.geneticalliance.org/ksc_assets/pdfs/conf06/ylecam_eurordis_genetic%20alliance.pdf). Anyway, these definitions are based on prevalence as most of rare diseases are

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chronic conditions. For malignant tumors as sub-acute illnesses, incidence is a better parameter to measure the number of cases occurring in a population. Therefore, the RARECARE Project, an international consensus group which was co-funded by the European Commission, defined rare cancers in adults by using incidence, setting the threshold for rarity at 6/100,000/year (Gatta et al. 2010).

4.2 Classification

The specific spectrum of rare cancers in children is not well described through one of the existing classification systems. The International Classification of Diseases for Oncology (ICD-O, 3rd edition) is primarily developed for adult cancers and based on tumor site (Fritz et al. 2000). The International Classification of Childhood Cancer (ICCC, 3rd edition) on the other hand is primarily based on morphology and histology (Steliarova-Foucher et al. 2005). A combination of both systems has to be used, the ICCC and ICD-O morphology and topography codes. This approach has been chosen for the here-presented analysis. While the ICCC was used to find a threshold for rare pediatric tumors, ICD-O morphology and topography codes were additionally applied in order to identify specific rare entities for further analysis. So far, no uniform classification system for rare pediatric entities has been defined. Anyway, there have been efforts to develop a separate nosologic system for malignant entities occurring in adolescents and young adults (Birch et al. 2002). This system might be used as a basis for the development of a new classification for pediatric rare tumors, which mainly occur in adolescents and therefore show a similar spectrum.

4.3 Definition and Incidence of Rare Tumors in Children in Different Countries

Cancer is a common disease. The risk of a person to develop a malignant disease during life is 38% for women and 47% for men. In children, though, cancer is generally rare according to the above-mentioned definitions. The annual incidence of cancer in the United States in children under the age of 15 years is 14 in 100,000 (Smith and Gloeckler Ries 2002). In Germany, around 16 of 100,000 children are diagnosed with cancer each year compared to 470/100,000 adults. The likelihood that a newborn is diagnosed with a malignant disease until its 15th birthday is 0.2% only (Robert Koch Institute and Association of Population-based Cancer Registries in Germany 2010). Anyway, clinicians realized that there are several entities occurring in children they might only see once in their lifetime practice but present a major problem as no definite guidelines for diagnosis and treatment exist for pediatric age. There have been several efforts to define these rare tumors in children. Realizing that we are actually dealing with not only very rare but also "orphan" entities, the Italian TREP project (Italian Study on Rare Tumors in Pediatric Age) pragmatically defined rare pediatric tumors as "any malignancies characterized by an annual incidence <2/million and not considered in other trials" (Ferrari et al. 2007). The German Rare Tumor group adopted this definition, when they launched their project in 2006 stressing one of the main goals to build up structures for rare tumors (Brecht et al. 2009). An analysis from the German Childhood Cancer Registry (GCCR) revealed 129 rare cases diagnosed between 1998 and 2007, and not being registered with one of the Society of Pediatric Oncology and Hematology (GPOH) studies (Brecht et al. 2010), the Italian TREP group registered 540 pediatric patients between January 2000 and December 2009 (see chapter on national rare tumor groups). Brennan used an arbitrary cutoff point and defined rare pediatric tumors as those which have "an age-standardized annual incidence of less than 1 per million children in the U.K., excluding tumors of unspecified morphology" registering 766 patients under the age of 15 years between 1991 and 2000 (see chapter on national rare tumor groups). Anyway, this definition excludes melanoma, which is the most common rare tumor seen in children and adolescents (Brennan and Stiller 2010). Pappo therefore stated that the United States Infrequent Tumor Initiative of the Children's Oncology Group basically deals with tumors "classified as other malignant epithelial neoplasms and melanomas in the International Classification of Childhood Cancer subgroup XI of the SEER database" being predominantly adult cancer occurring in pediatric age (Pappo et al. 2010). According to this definition, rare tumors compose approximately 15% of all cancers in the age group <15 years and 30% in <20 years (see chapter on national rare tumor groups). In conclusion, a comprehensive definition of rare pediatric tumors could be:

Rare pediatric malignancies are characterized by an annual incidence <2/1,000,000 and/or are considered as "orphan" due to lack of pediatric trials and/or underestimation of incidence. Rare pediatric malignancies might be common in adult age or pediatric subpopulations like a specific age group, a country or a gender, often an underlying genetic predisposition can be suspected, and they might be inadequately diagnosed and treated.

4.4 Data from the United States Surveillance, Epidemiology, and End Results Database (SEER): How Rare Are Rare Tumors?

We face great difficulties to define the exact incidence of rare pediatric tumors. Problems arise from the rarity of the entities. Because of lacking experience with these tumor types, there might be diagnostic and coding inconsistencies (Pastore et al. 2009). For example, the incidence of pleuropulmonary blastoma might be underestimated if they are registered as sarcomas in population-based registries. Also, the classification of entities into benign, borderline, and malignant neoplasms might not be uniform (Stiller 2007). Some patients with rare tumors might not be reported to registries for reasons lying in the organizational structures of pediatric oncology within different countries. In the German Childhood Cancer Registry (GCCR), approximately 1,800 newly diagnosed children up to 15 years of age are registered annually (Kaatsch and Spix 2008). More than 95% of these patients are enrolled into the therapeutic optimization study of the respective tumor group, either as regular protocol patients or as follow-up patients within these clinical registries. Rare tumors on the other hand usually are not registered in clinical trials and often are treated in adult oncology departments and other disciplines like ENT and dermatology. They are therefore not integrated in the close network of the Pediatric Societies (Brecht et al. 2009). Also, the incidence of rare pediatric tumors rises in adolescence, while pediatric cancer registries have a tradition to register children under the age of 15 years only. In Germany, the GCCR started to register children up to 18 years of age in 2010 only. We have to conclude that the incidence of rare tumors in children and adolescents so far is underestimated and largely unknown. Most entities therefore have to be considered to be "orphan."

The Surveillance, Epidemiology, and End Results (SEER) database of the U.S. National Cancer Institute registers patients with cancer of all age groups. Data is provided by 18 registries accounting for 10–14% of the United States population during the study period from 1973 to 2004 (SEER 2007) and by 13 registries during the study period from 1992 to 2007 (SEER 2010). We used data from the SEER database collected between 1992 and 2007 to get a more realistic overview of rare tumor entities in childhood and adolescence. According to the above-provided definition for rare pediatric tumors, we included all children and adolescents under the age of 20 years with an extracranial solid tumor that has an incidence rate of <2/1,000,000 in the age group <15 years and/or <20 years in this analysis. Data were sorted by ICCC-3 and ICD-O3 (see Tables 4.1 and 4.2); 2,887 patients with a rare extracranial tumor were identified within the age group 0–14 years and 6,923 patients within the age group 0–19 years. The age-specific incidence rate of rare pediatric tumors in the United States was calculated to be 21.1/1,000,000 under the age of 15 years and 37.6/1,000,000 under the age of 20 years. Table 4.1 shows age-specific incidence rates and percentages of rare tumors. In the age group 0–14 years, rare tumors account for 14% of all cancer cases and in the age group 0–19 years, 24%. Anyway, these numbers include germ cell tumors and rare soft tissue sarcomas, which are registered in pediatric clinical trials in most developed countries and therefore are not considered as rare pediatric tumors according to the above-mentioned definition. If rare soft tissue sarcomas and germ cell tumors are excluded, the incidence rate of rare pediatric tumors usually not registered in clinical trials is 11.5/1,000,000 under the age of 15 years (8% of all cancers in that age group) and 21.3/1,000,000 under the age of 20 years (14% of all cancers in that age group). Consequently, surprisingly high numbers of children and adolescents with rare tumors can be identified through the SEER database.

4.4.1 Entity-Specific Incidence

Though rare tumor entities account for a surprisingly high percentage of all malignant entities in childhood and adolescents, the incidence of single histologic entities obviously is extremely low. We used data from the SEER database collected between 1973 and 2004 and 1992 and 2007 (SEER 2007). In order to get a detailed overview of

Table 4.1 Annual incidence of pediatric cancer and rare pediatric malignant tumors within different age groups (Data from the United States Surveillance, Epidemiology, and End Results database (1992–2007) (rare tumors defined as all extracranial solid tumors with an incidence rate of <2/1,000,000 in the age group <15 years and/or <20 years), excluded hematopoietic cancers)

	00–14 years		00–19 years		00–04 years		05–09 years		10–14 years		15–19 years	
United States population	134,900,815		177,623,103		45,673,629		44,723,693		44,503,493		42,722,288	
	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
Incidence of all malignant cancer[1]	152.19	19,984	164.58	28,838	206.75	9,445	110.57	4,945	125.7	5,594	207.25	8,854
Incidence of all malignant solid tumors[2]	87.12	11,424	96.98	17,019	121.44	5,552	58.49	2,616	73.16	3,256	130.96	5,595
Incidence of rare malignant solid tumors[2]	21.06	2,887	37.55	6,923	20.94	958	11.46	516	31.7	1,413	94.47	4,036
Percentage of rare entities of all malignant cancer	14		24		10		10		25		46	
Percentage of rare entities of all malignant solid tumors	25		41		17		20		43		72	
Incidence of rare malignant solid tumors excluding germ cell tumors and rare soft tissue sarcomas	11.53	1,599	21.33	3,952	10.04	459	6.77	305	18.72	835	55.08	2,353
Percentage of rare entities not registered in clinical studies of all malignant cancer	8		14		5		6		15		27	
Percentage of rare entities not registered in clinical studies of all malignant solid tumors	14		23		8		11		26		42	

[1]including hematopoietic cancers
[2]excluding hematopoietic cancers

different rare entities found in that age group, we applied the ICD-O for histology and topography to rare tumor types identified and defined above. Table 4.2 shows the number of cases and incidence rate of all extracranial solid tumors with an incidence rate of <2/1,000,000 in the age group <15 years and/or <20 years sorted by ICCC-3 and ICD-O3 and registered within the United States Surveillance, Epidemiology, and End Results database (1992–2007). Figures 4.1–4.7 show the distribution of rare entities within the ICCC groups IV (Rare tumors of the peripheral nervous cell tumors), VI (Rare renal tumors), VII (Hepatic tumors), VIII (Malignant bone tumors), IX (Rare soft tissue and other extraosseous sarcomas), X (Germ cell tumors, trophoblastic tumors, and

Table 4.2 Rare tumors in children and adolescents: number of cases and annual incidence rate of all extracranial solid tumors (hematopoietic cancers excluded) with an incidence rate of <2/1,000,000 in the age group <15 years and/or <20 years sorted by ICCC (3rd edition) and ICD-O (3rd edition) and registered within the United States Surveillance, Epidemiology, and End Results database (1992–2007)

Age at diagnosis (years)	00–14 years		00–19 years		00–04 years		05–09 years		10–14 years		15–19 years	
International classification of childhood cancer (3rd edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
IV Rare tumors of the peripheral nervous cell tumors												
IV(b) Other peripheral nervous cell tumors	0.19	26	0.26	47	0.15	7	0.18	8	0.25	11	0.49	21
VI Rare renal tumors												
VI(a.2) Rhabdoid renal tumor	0.20	24	0.16	24	0.50	23	0.02	1	0.00	0	0.00	0
VI(a.3) Kidney sarcomas	0.28	34	0.22	35	0.64	29	0.11	5	0.00	0	0.02	1
VI(b) Renal carcinomas	0.25	36	0.48	91	0.11	5	0.20	9	0.49	22	1.29	55
VII Hepatic tumors												
VII(a) Hepatoblastoma	**2.36**	282	1.83	282	**5.68**	260	0.40	18	0.09	4	0.00	0
VII(b) Hepatic carcinomas	0.36	52	0.59	110	0.18	8	0.27	12	0.72	32	1.36	58
VII(c) Unspecified malignant hepatic tumors	0.03	3	0.02	3	0.07	3	0.00	0	0.00	0	0.00	0
VIII Malignant bone tumors												
VIII(b) Chondrosarcomas	0.19	29	0.33	64	0.00	0	0.07	3	0.58	26	0.82	35
VIII(c.1) Ewing tumor and Askin tumor of bone	1.66	239	**2.27**	426	0.55	25	1.61	72	**3.19**	142	**4.38**	187
VIII(c.2) pPNET of bone	0.10	15	0.13	25	0.00	0	0.13	6	0.20	9	0.23	10
VIII(d.1) Malignant fibrous neoplasms of bone	0.04	5	0.07	13	0.07	3	0.04	2	0.00	0	0.19	8
VIII(d.2) Malignant chordomas	0.15	21	0.23	43	0.11	5	0.20	9	0.16	7	0.51	22
VIII(d.3) Odontogenic malignant tumors	0.01	2	0.06	11	0.00	0	0.04	2	0.00	0	0.21	9
VIII(d.4) Miscellaneous malignant bone tumors	0.06	9	0.09	17	0.02	1	0.02	1	0.16	7	0.19	8
VIII(e) Unspecified malignant bone tumors	0.06	9	0.09	17	0.04	2	0.02	1	0.13	6	0.19	8

(continued)

Table 4.2 (continued)

Age at diagnosis (years)	00–14 years		00–19 years		00–04 years		05–09 years		10–14 years		15–19 years	
International classification of childhood cancer (3rd edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
IX Rare soft tissue and other extraosseous sarcomas												
IX(b.1) Fibroblastic and myofibroblastic tumors	0.80	102	0.79	134	1.41	65	0.31	14	0.52	23	0.75	32
IX(b.2) Nerve sheath tumors	0.44	63	0.57	108	0.20	9	0.25	11	0.97	43	1.05	45
IX(b.3) Other fibromatous neoplasms	0.01	1	0.01	2	0.00	0	0.02	1	0.00	0	0.02	1
IX(c) Kaposi sarcoma	0.02	3	0.05	9	0.02	1	0.04	2	0.00	0	0.14	6
IX(d.1) Ewing tumor and Askin tumor of soft tissue	0.35	49	0.46	85	0.20	9	0.29	13	0.61	27	0.84	36
IX(d.2) pPNET of soft tissue	0.26	36	0.32	59	0.20	9	0.29	13	0.31	14	0.54	23
IX(d.3) Extrarenal rhabdoid tumor	0.22	27	0.17	28	0.44	20	0.04	2	0.11	5	0.02	1
IX(d.4) Liposarcomas	0.12	18	0.29	55	0.04	2	0.11	5	0.25	11	0.87	37
IX(d.5) Fibrohistiocytic tumors	0.94	133	1.33	247	0.59	27	0.65	29	1.73	77	**2.67**	114
IX(d.6) Leiomyosarcomas	0.18	25	0.26	48	0.11	5	0.25	11	0.20	9	0.54	23
IX(d.7) Synovial sarcomas	0.59	88	0.96	184	0.11	5	0.29	13	1.57	70	**2.25**	96
IX(d.8) Blood vessel tumors	0.08	11	0.12	22	0.11	5	0.04	2	0.09	4	0.26	11
IX(d.9) Osseous and chondromatous neoplasms of soft tissue	0.08	11	0.11	21	0.02	1	0.07	3	0.16	7	0.23	10
IX(d.10) Alveolar soft parts sarcoma	0.08	12	0.12	23	0.04	2	0.04	2	0.18	8	0.26	11
IX(d.11) Miscellaneous soft tissue sarcomas	0.22	31	0.22	41	0.15	7	0.13	6	0.40	18	0.23	10
IX(e) Unspecified soft tissue sarcomas	0.77	108	1.03	190	0.55	25	0.49	22	1.37	61	1.92	82
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads												

Table 4.2 (continued)

Age at diagnosis (years)	00–14 years		00–19 years		00–04 years		05–09 years		10–14 years		15–19 years	
International classification of childhood cancer (3rd edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
X(b.1) Germinomas: extracranial/ extragonadal	0.08	11	0.18	34	0.07	3	0.02	1	0.16	7	0.54	23
X(b.2) Malignant teratomas: extracranial/ extragonadal	1.09	130	0.88	138	**2.70**	124	0.09	4	0.04	2	0.19	8
X(b.3) Embryonal carcinomas: extracranial/ extragonadal	0.00	0	0.01	1	0.00	0	0.00	0	0.00	0	0.02	1
X(b.4) Yolk sac tumor: extracranial/ extragonadal	0.54	65	0.45	70	1.31	60	0.04	2	0.07	3	0.12	5
X(b.5) Choriocarcinomas: extracranial/ extragonadal	0.02	3	0.19	37	0.00	0	0.00	0	0.07	3	0.80	34
X(b.6) Other mixed germ cell: extracranial/ extragonadal	0.09	11	0.14	25	0.20	9	0.00	0	0.04	2	0.33	14
X(c.1) Malignant gonadal germinomas	0.37	55	1.34	255	0.04	2	0.29	13	0.90	40	**4.68**	200
X(c.2) Malignant gonadal teratomas	0.85	121	1.86	348	0.52	24	0.60	27	1.57	70	**5.31**	227
X(c.3) Gonadal embryonal carcinomas	0.06	8	0.77	145	0.07	3	0.00	0	0.11	5	**3.21**	137
X(c.4) Gonadal yolk sac tumor	0.77	95	0.85	144	1.60	73	0.16	7	0.34	15	1.15	49
X(c.5) Gonadal choriocarcinoma	0.01	1	0.09	17	0.00	0	0.02	1	0.00	0	0.37	16
X(c.6) Malignant gonadal tumors of mixed forms	0.33	48	2.14	406	0.13	6	0.07	3	0.88	39	**8.38**	358
X(c.7) Malignant gonadal gonadoblastoma	0.00	0	0.01	1	0.00	0	0.00	0	0.00	0	0.02	1
X(d) Gonadal carcinomas	0.07	10	0.35	66	0.00	0	0.00	0	0.22	10	1.31	56
X(e) Other and unspecified malignant gonadal tumors	0.09	12	0.15	28	0.07	3	0.09	4	0.11	5	0.37	16

(continued)

Table 4.2 (continued)

Age at diagnosis (years)	00–14 years		00–19 years		00–04 years		05–09 years		10–14 years		15–19 years	
International classification of childhood cancer (3rd edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
XI Other malignant epithelial neoplasms and malignant melanomas												
XI(a) Adrenocortical carcinomas	0.24	31	0.26	44	0.39	18	0.16	7	0.13	6	0.30	13
XI(b) Thyroid carcinomas	1.75	262	**5.18**	989	0.04	2	1.16	52	**4.67**	208	**17.02**	727
XI(c) Nasopharyngeal carcinomas	0.20	31	0.48	92	0.00	0	0.02	1	0.67	30	1.43	61
XI(d) Malignant melanomas	1.59	229	**4.63**	874	0.66	30	1.23	55	**3.24**	144	**15.10**	645
XI(e) Skin carcinomas	0.06	9	0.08	16	0.02	1	0.02	1	0.16	7	0.16	7
XI(f.1) Carcinomas of salivary glands	0.43	64	0.76	145	0.07	3	0.20	9	1.17	52	1.90	81
XI(f.2) Carcinomas of colon and rectum	0.12	18	0.49	94	0.00	0	0.02	1	0.38	17	1.78	76
XI(f.3) Carcinomas of appendix	0.06	9	0.14	27	0.00	0	0.00	0	0.20	9	0.42	18
XI(f.4) Carcinomas of lung	0.11	16	0.25	47	0.02	1	0.04	2	0.29	13	0.73	31
XI(f.5) Carcinomas of thymus	0.04	6	0.06	11	0.00	0	0.04	2	0.09	4	0.12	5
XI(f.6) Carcinomas of breast	0.04	6	0.19	36	0.00	0	0.00	0	0.13	6	0.70	30
XI(f.7) Carcinomas of cervix uteri	0.02	3	0.23	43	0.00	0	0.04	2	0.02	1	0.94	40
XI(f.8) Carcinomas of bladder	0.02	3	0.08	15	0.02	1	0.00	0	0.04	2	0.28	12
XI(f.9) Carcinomas of eye	0.02	3	0.02	4	0.02	1	0.02	1	0.02	1	0.02	1
XI(f.10) Carcinomas of other specified sites	0.40	58	0.93	176	0.15	7	0.27	12	0.88	39	**2.76**	118
XI(f.11) Carcinomas of unspecified site	0.09	13	0.20	37	0.07	3	0.00	0	0.22	10	0.56	24
XII(a.1) Gastrointestinal stromal tumor	0.04	5	0.05	10	0.02	1	0.02	1	0.07	3	0.12	5
XII(a.2) Pancreatoblastoma	0.03	5	0.03	6	0.00	0	0.07	3	0.04	2	0.02	1

Table 4.2 (continued)

Age at diagnosis (years)	00–14 years		00–19 years		00–04 years		05–09 years		10–14 years		15–19 years	
International classification of childhood cancer (3rd edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
XII(a.3) Pulmonary blastoma and pleuropulmonary blastoma	0.10	12	0.08	13	0.22	10	0.00	0	0.04	2	0.02	1
XII(a.4) Other complex mixed and stromal neoplasms	0.03	4	0.05	9	0.00	0	0.02	1	0.07	3	0.12	5
XII(a.5) Mesothelioma	0.00	0	0.02	4	0.00	0	0.00	0	0.00	0	0.09	4
XII(a.6) Other specified malignant tumors	0.01	1	0.01	1	0.00	0	0.00	0	0.02	1	0.00	0
XII(b) Other unspecified malignant tumors	0.19	25	0.28	51	0.22	10	0.13	6	0.20	9	0.61	26
Sum	21.06	2887	37.55	6923	20.94	958	11.46	516	31.7	1413	94.47	4036

Incidence rates of >2/1,000,000 within specific age groups are marked in bold

neoplasms of gonads), and XI (Other malignant epithelial neoplasms and malignant melanomas).

4.4.2 Age-Specific Incidence

The overall incidence of rare tumors rises dramatically within adolescence (Table 4.2, Figs. 4.8–4.11). As shown in Table 4.2, rare tumors account for 5% of all malignant entities within the age group 0–4 years; within the age group of 15–19 years, this number rises up to 27% already. This is mainly due to a rise in the registration of malignant melanoma, carcinoma, and rare gonadal tumors. A publication from the public population-based Surveillance, Epidemiology, and End Results (SEER) database of the U.S. National Cancer Institute estimates that rare tumors in adolescents between 15 and 19 years – meaning patients for which no specific pediatric therapeutic trials are available – already account for 23% of all malignancies in this age group (Ries et al. 1999). Also, the European Automated Childhood Cancer Information System (ACCIS) reports an incidence of carcinomas of 3.4/100,000 in the age group 0–14 years, but 9.9/100,000 in children and adolescents up to 19 years (http://wwwdep.iarc.fr/accis.htm). On the other hand, some few rare entities typically occur in early childhood. An example is the hepatoblastoma, which basically only occurs within the first years of life (Fig. 4.12).

4.5 Conclusion

"Rare" is not a uniform expression. A malignant tumor can be rare in childhood and adolescence for a large variety of reasons. The incidence of a discrete entity can be low within all children and adolescents all over the world, equally in female and male – or the tumor might be rare because we are looking at a sub-population like a specific age group or country, a gender, a histological sub-entity, or even a specific tumor site the entity is occurring in. These so-defined rare tumors might be identified to be rare through only one characteristic but actually might show also other differences, e.g., tumor biology and behavior, and therefore constitute a separate entity.

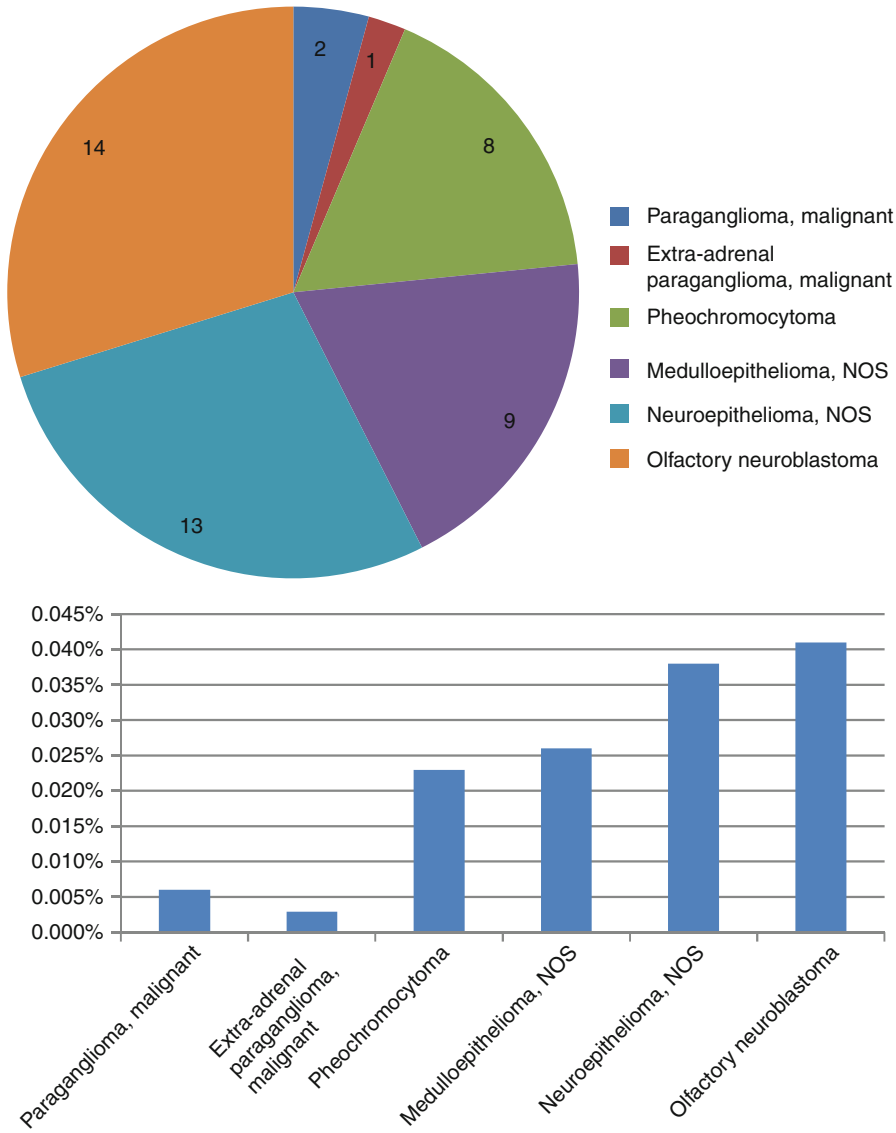

Fig. 4.1 Absolute number and percentage of rare tumors of the peripheral nervous system (n = 47) of all malignant entities in children under the age of 15 years (including hematopoietic cancers, n = 34494). (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

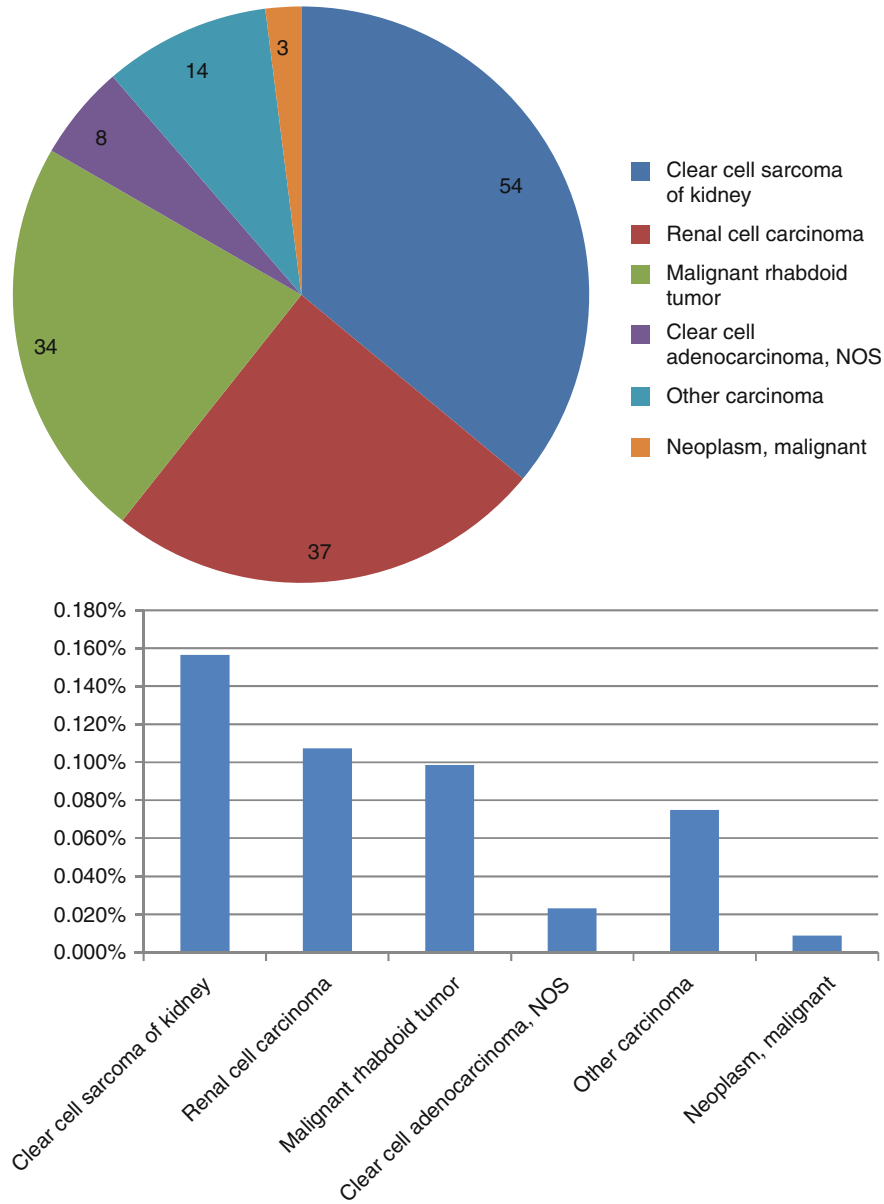

Fig. 4.2 Absolute number and percentage of rare renal tumors (n = 150) of all malignant entities in children under the age of 15 years (including hematopoietic cancers, n = 34494). (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

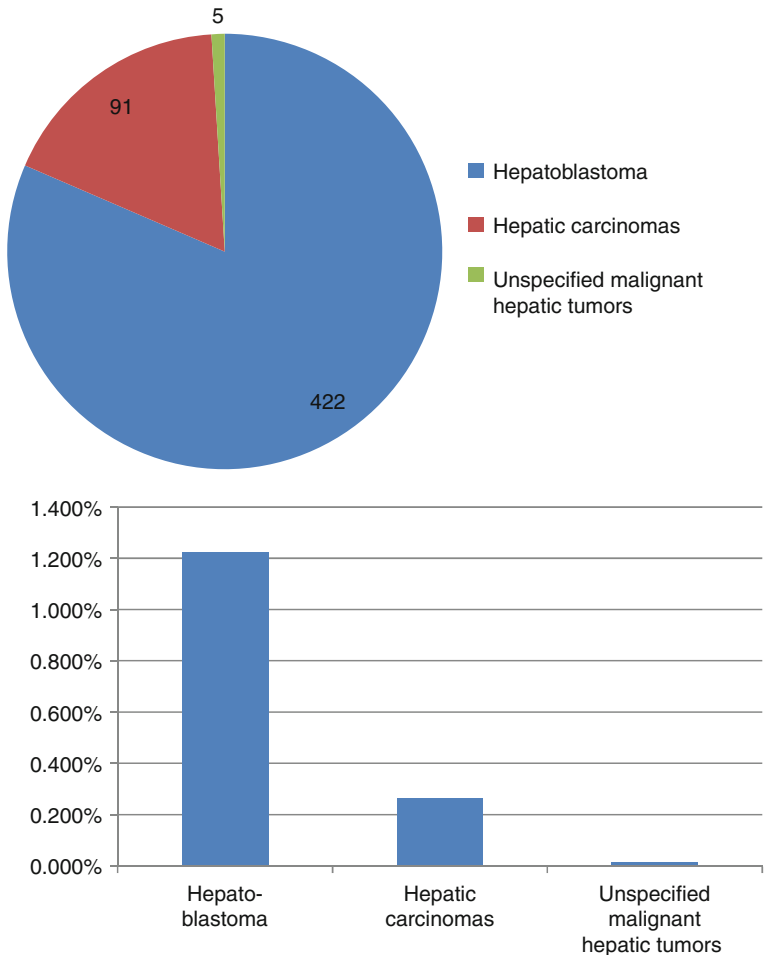

Fig. 4.3 Absolute number and percentage of rare hepatic tumors (n = 518) of all malignant entities in children under the age of 15 years (including hematopoietic cancers, n = 34494). (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

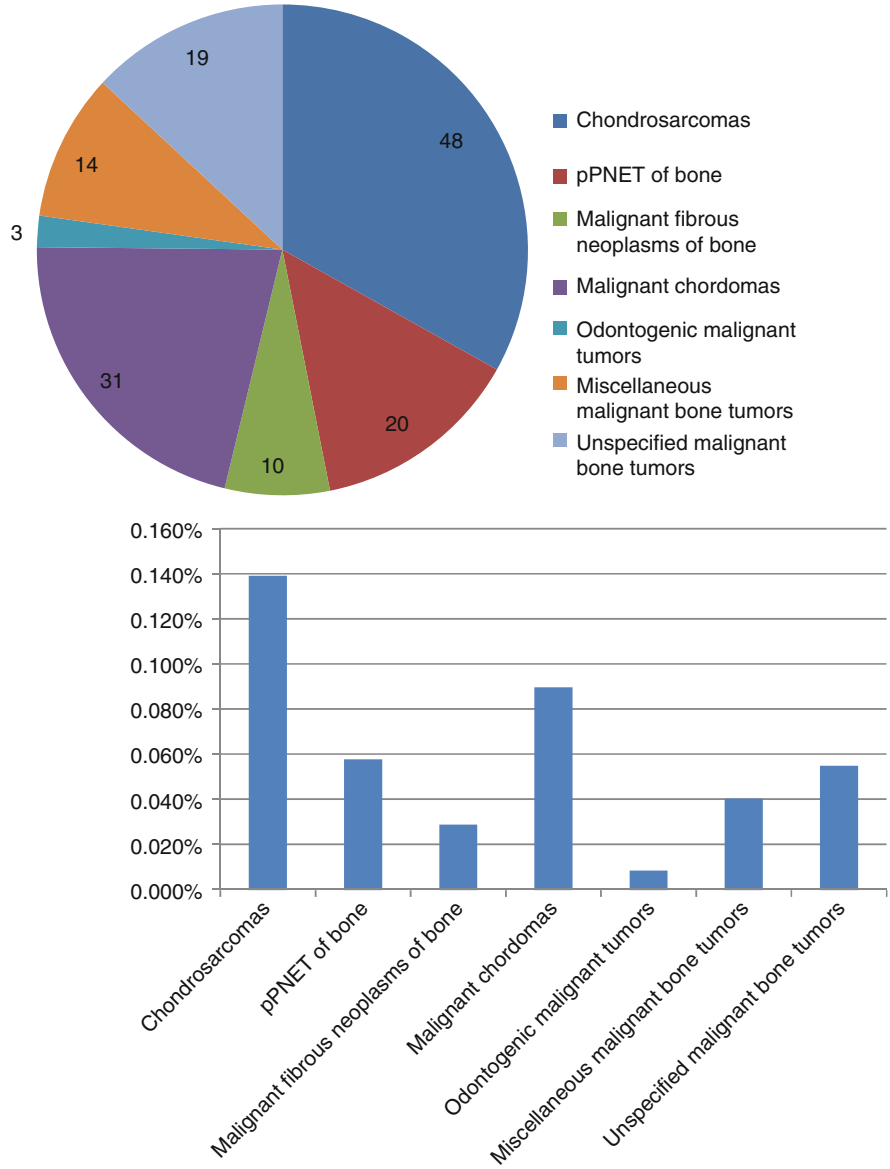

Fig. 4.4 Absolute number and percentage of rare bone tumors (n = 48) of all malignant entities in children under the age of 15 years (including hematopoietic cancers, n = 34494). (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

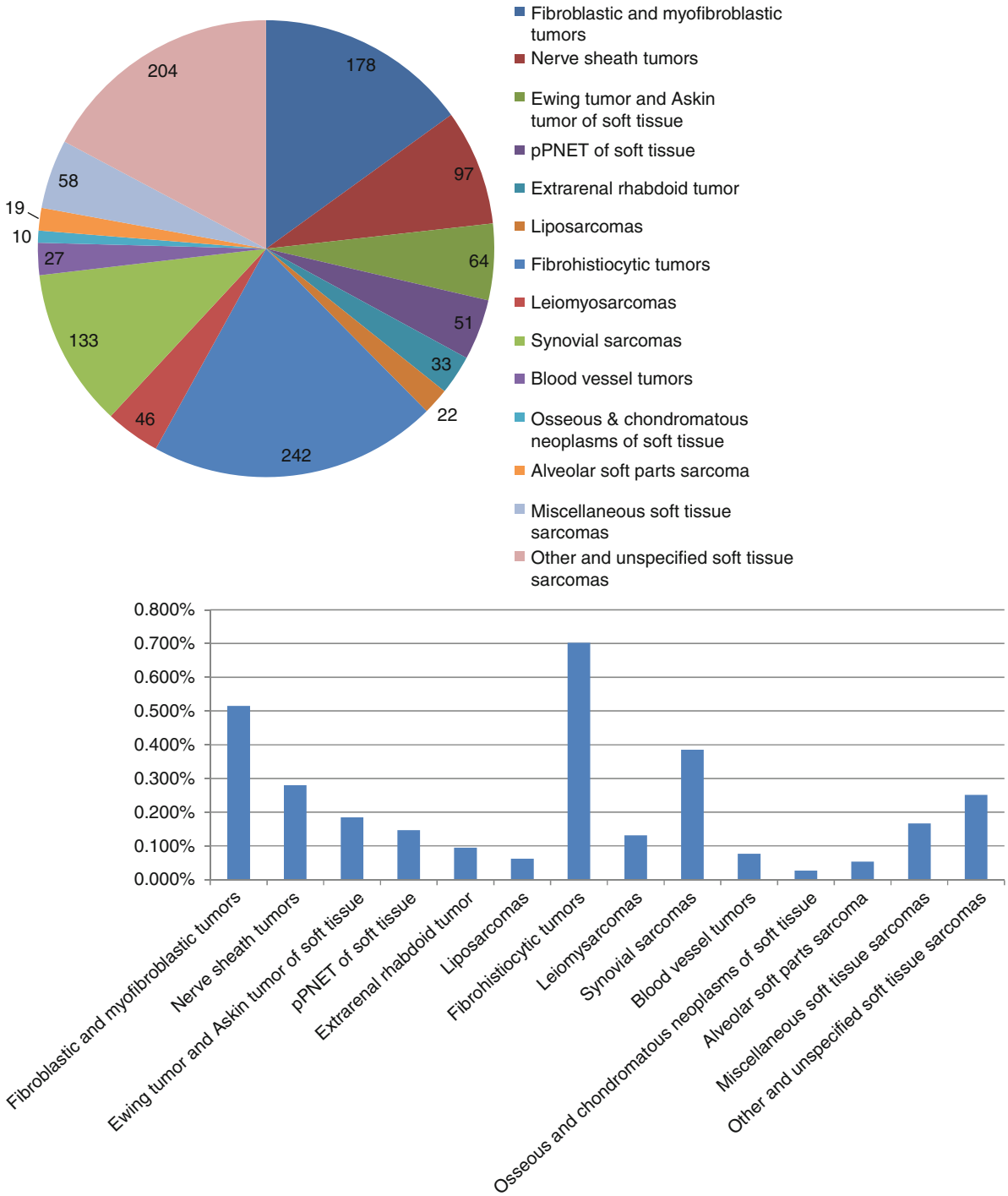

Fig. 4.5 Absolute number and percentage of rare soft tissue tumors (n = 1184) of all malignant entities in children under the age of 15 years (including hematopoietic cancers, n = 34494). (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

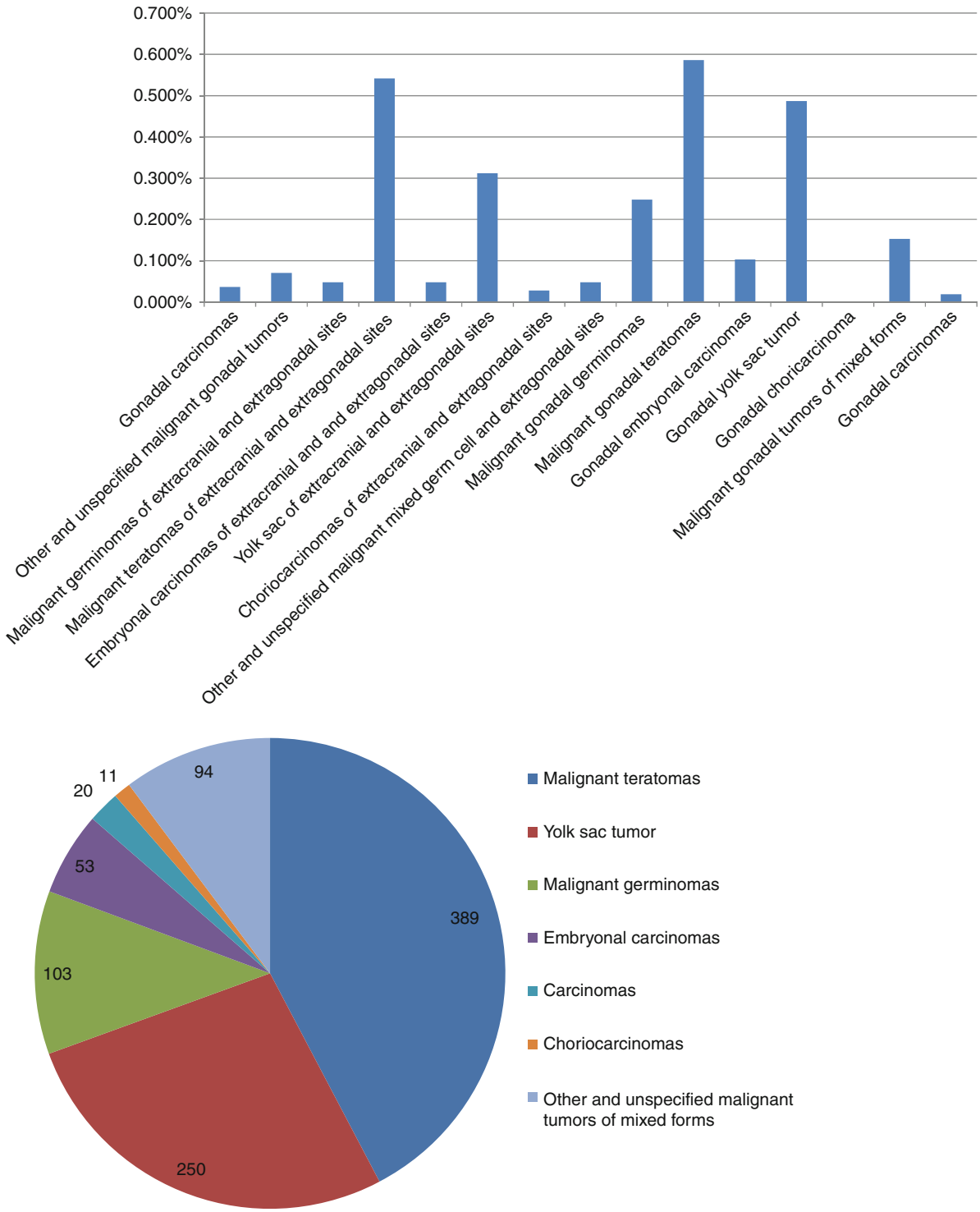

Fig. 4.6 Absolute number and percentage of germ cell tumors (n = 920) of all malignant entities in children under the age of 15 years (including hematopoietic cancers, n = 34494). (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

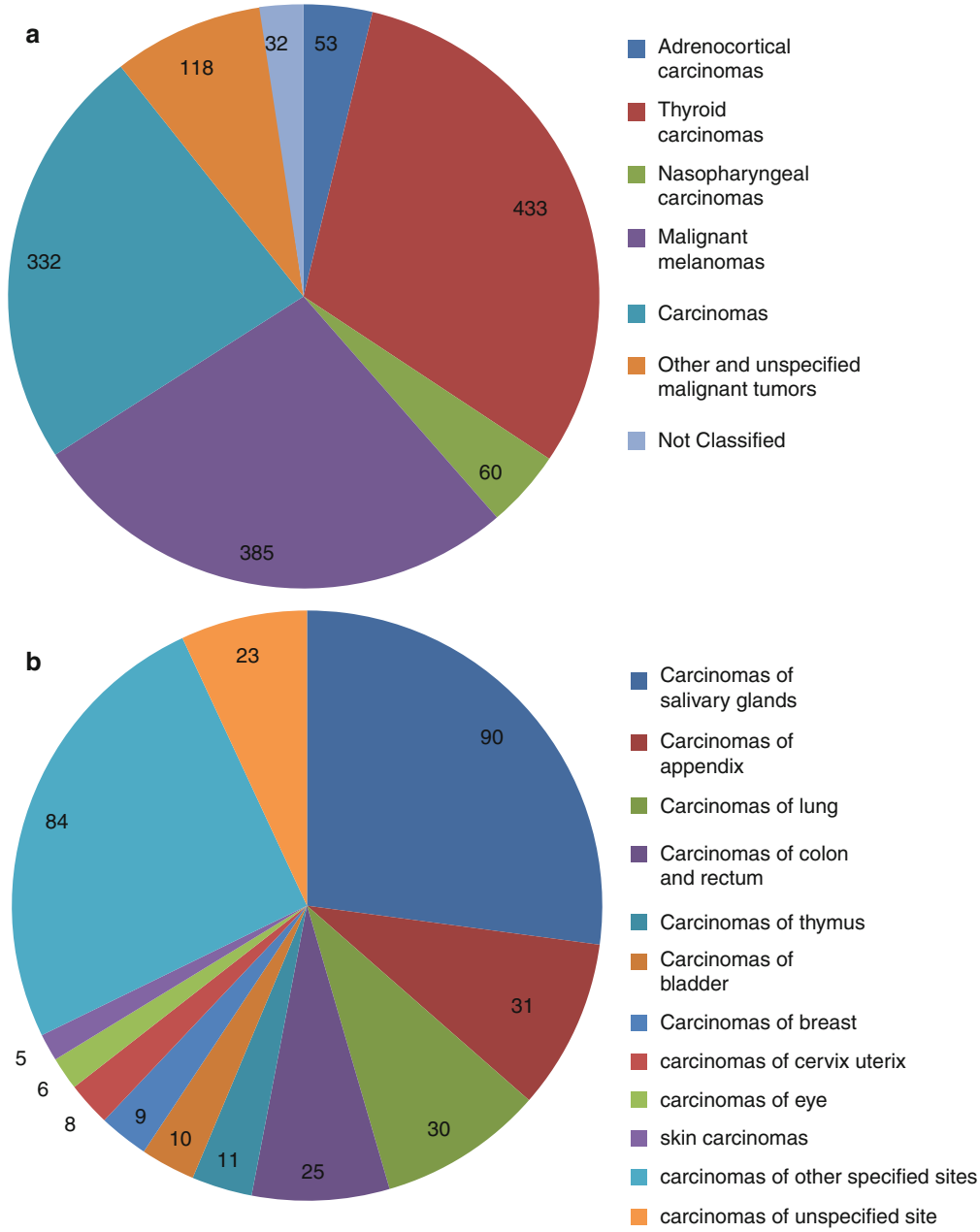

Fig. 4.7 (**a**) Absolute number of other malignant epithelial neoplasms and melanomas in children under the age of 15 years (n = 1,413). For detailed information on carcinomas see (**c**). (**b**) Absolute number of carcinomas in children under the age of 15 years (n = 332). (**c**) Percentage of other malignant epithelial neoplasms and melanomas (n = 1,413) of all malignant entities in children under the age of 15 years (including hematopoietic cancers, n = 34,494) (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

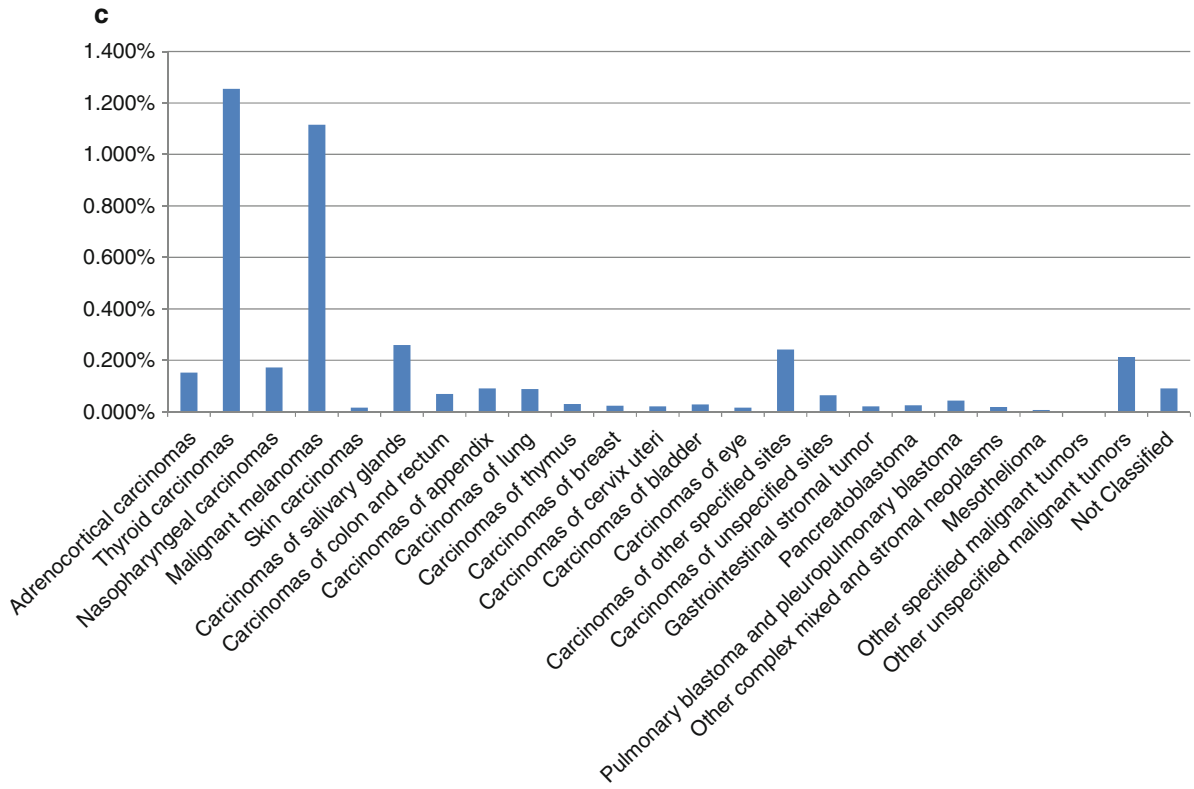

Fig. 4.7 (continued)

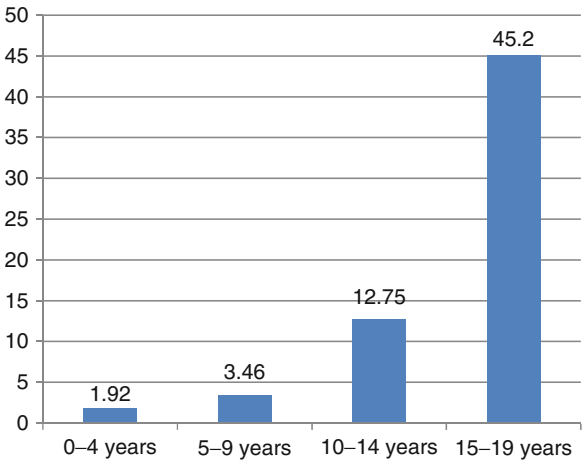

Fig. 4.8 Distribution of other malignant epithelial neoplasms and malignant melanoma over different age groups. Incidence rates per 1,000,000 are provided. (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

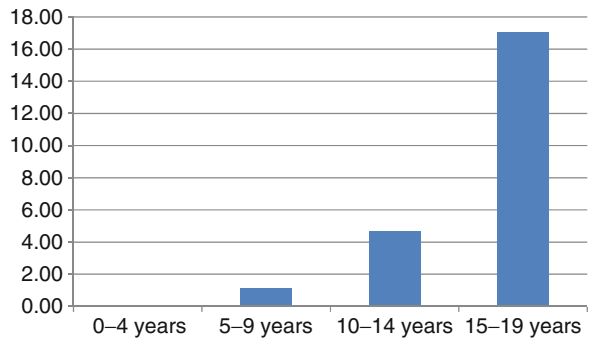

Fig. 4.9 Distribution of thyroid carcinoma over different age groups. Incidence rates per 1,000,000 are provided. (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

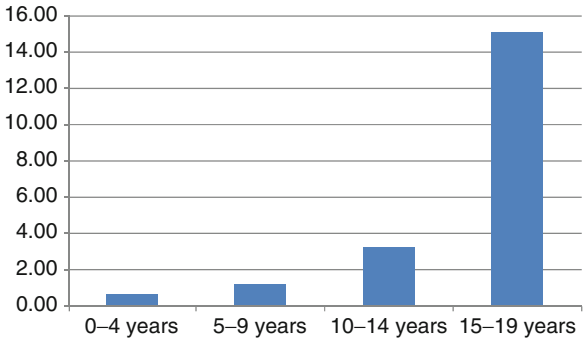

Fig. 4.10 Distribution of melanoma over different age groups. Incidence rates per 1,000,000 are provided. (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

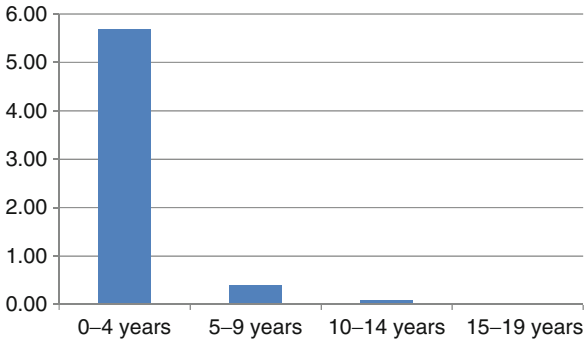

Fig. 4.11 Distribution of hepatoblastoma over different age groups. Incidence rates per 1,000,000 are provided. (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

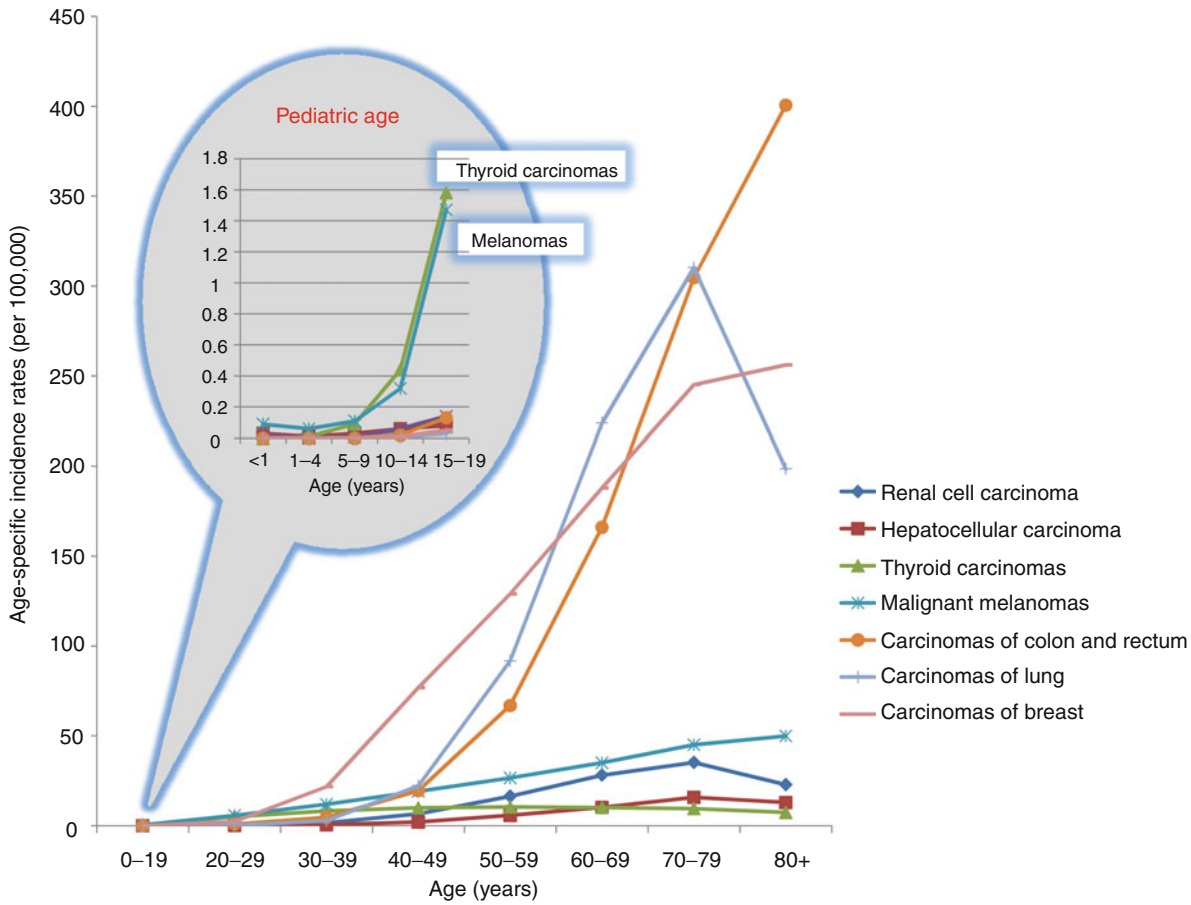

Fig. 4.12 Age-specific incidence rates (per 100,000 population) of selected adult cancers from the United States Surveillance, Epidemiology and End Results database (1973–2006). (Courtesy Dr. Sultan, Dr. Ferrari)

References

Birch JM, Alston RD et al (2002) Classification and incidence of cancers in adolescents and young adults in England 1979–1997. Br J Cancer 87(11):1267–1274

Brecht IB, Graf N et al (2009) Networking for children and adolescents with very rare tumors: foundation of the GPOH Pediatric Rare Tumor Group. Klin Padiatr 221(3):181–185

Brecht I, Bremensdorfer C et al (2010) Incidence of rare malignant pediatric tumors in Germany 1998–2007: data from the German Childhood Cancer Registry. Pediatr Blood Cancer 55:909

Brennan B, Stiller C (2010) Rare tumors. In: Estlin EJ, Gilbertson RJ, Wynn RF (eds) Pediatric hematology and oncology. Blackwell Publishing Ltd.

Ferrari A, Bisogno G et al (2007) The challenge of very rare tumours in childhood: the Italian TREP project. Eur J Cancer 43(4):654–659

Fritz AG, Percy C et al (2000) International classification of diseases for oncology (ICD-O), 3rd edn. World Health Organization, Geneva

Gatta G, Capocaccia R et al (2010) The burden of rare cancers in Europe. Adv Exp Med Biol 686:285–303

Kaatsch P, Spix P (2008) Annual report of the German Childhood Cancer Registry 2006/2007. www.kinderkrebsregister.de

National Institutes of Health (2010) National Institutes of Health. Office of rare disease research. Rare diseases and related terms. http://rarediseases.info.nih.gov/RareDiseaseList.aspx. Retrieved 28 Feb 2011

Pappo AS, Krailo M et al (2010) Infrequent tumor initiative of the Children's Oncology Group: initial lessons learned and their impact on future plans. J Clin Oncol 28(33):5011–5016

Pastore G, De Salvo GL et al (2009) Evaluating access to pediatric cancer care centers of children and adolescents with rare tumors in Italy: the TREP project. Pediatr Blood Cancer 53(2):152–155

Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL et al (1999) Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. NIH Pub No.99–4649

Robert Koch Institute and Association of Population-based Cancer Registries in Germany (ed) (2010) Cancer in Germany 2005/2006. Incidence and trends. Robert Koch Institute and Association of Population-based Cancer Registries in Germany, Berlin

Smith M, Gloeckler Ries L (2002) Childhood cancer: incidence, survival and mortality. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology, 4th edn. Lippincott Williams & Wilkins, Philadelphia

Steliarova-Foucher E, Stiller C et al (2005) International classification of childhood cancer, third edition. Cancer 103(7):1457–1467

Stiller CA (2007) International patterns of cancer incidence in adolescents. Cancer Treat Rev 33(7):631–645

Surveillance, Epidemiology, and End Results (SEER) Program Populations (1973–2004) (2007) (www.seer.cancer.gov/popdata), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released 2007

Surveillance, Epidemiology, and End Results (SEER) Program Populations (1992–2007) (2010) (www.seer.cancer.gov/popdata), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released 2010.

Biology and Etiology of Rare Pediatric Tumors

5

Ines B. Brecht and Johannes H.M. Merks

Contents

5.1 Introduction

Different malignant tumor types occur in children compared to adults. While in childhood we typically find leukemia, lymphoma, and various embryonal tumors, in adulthood, mainly gastrointestinal cancer, melanoma, malignancies of the head and neck, and lung and breast cancers occur. Not only tumor types and frequency differs, also the pathogenetic origin and genetic factors in malignant childhood tumors are unlike those in adult cancer. Cancer biology changes over age as the inner and outer circumstances at the time of cancer initiating mutation vary according to state of development. Neoplasia in childhood and adolescence are mainly based on an intrinsic system error – mislead development within embryogenesis. These are often very simple but specific DNA, chromosome, or genomic rearrangements. Epithelial tumors and other adult-type tumors like secondary leukemia on the other hand show more complex genetic alterations. A long history of carcinogenic and mutagenic exposition, as well as mislead differentiation, aging, and elimination processes are involved in carcinogenesis in adulthood. These differences might also explain why childhood cancer is more responsive to therapy than adult cancer (Haas 2004).

5.2 Rare Pediatric Tumors

Also in children, we rarely find malignancies of adult age (see Fig. 5.1). These are mainly carcinomas of the head and neck, malignancies of the gastrointestinal tract, and melanoma. Because of the rarity of these entities within childhood, most clinicians are unsure about the biological and clinical characteristics and thus

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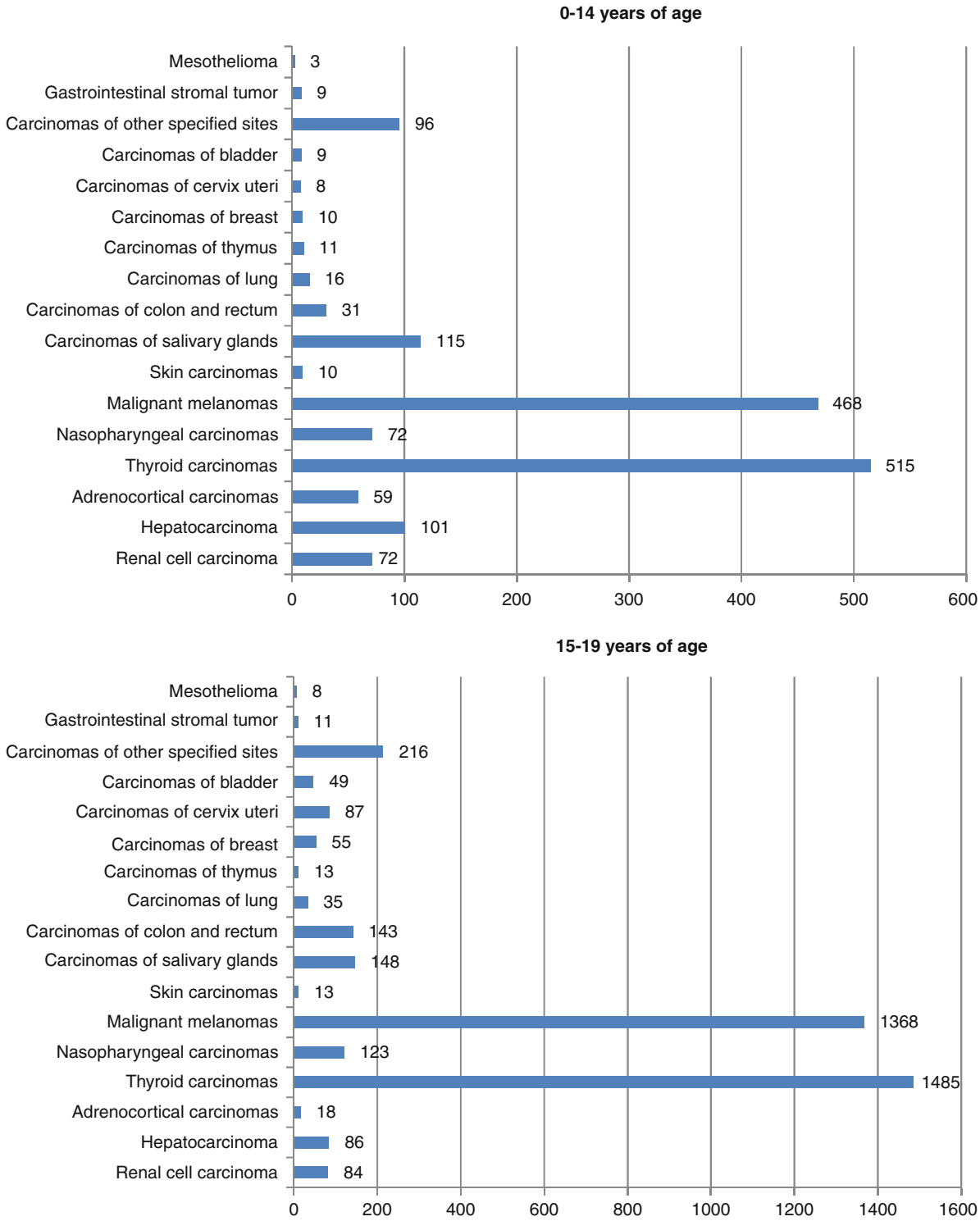

Fig. 5.1 Adult cancers occurring in childhood and adolescence: number of cases registered in the US Surveillance, Epidemiology and End Results (SEER) Date Base (1973–2006)

management within young ages. We understand that we deal with four different groups of rare tumors in childhood (see Introduction and Fig. 5.1). These are:

(a) Characteristic malignant tumors of childhood with generally extremely low incidence, e.g., pancreaticoblastoma or mesoblastic nephroma
(b) Malignant tumors, which might be diagnosed both during childhood and adolescence, which might be clinically and pathologically undistinguishable but biologically different, e.g., germ cell tumors
(c) Characteristic adult cancers, which are rarely diagnosed during childhood or adolescence presenting as the left edge of the Gauss distribution curve of a frequent adult cancer but still possibly showing biological and clinical characteristics different from adulthood, e.g., colon carcinoma, malignant melanoma
(d) Specific subentities of adult cancer types – hidden in the left edge of the Gauss distribution curve – with postulated distinct genetics and biology, e.g., underlying hereditary cancer syndromes.

5.3 Etiological and Biological Characteristics of Rare Pediatric Tumors

Little is known about the etiopathogenesis of rare tumors as there are several barriers for biological studies resulting from the rarity. Anyway, for many reasons, it is likely that we deal with very different tumorigenic mechanisms in rare pediatric tumors compared to classical tumors of childhood or adulthood. While for most typical childhood cancers it seems that prognosis declines with age, as shown for ALL and Ewing sarcoma (Rivera et al. 1993; Perentesis 1997; Cotterill et al. 2000), there is the impression that adult cancer shows a more aggressive behavior in childhood (Ferrari et al. 2010). In adulthood, these malignant tumors occur as a result of genetic changes following many years of exposure to carcinogens, but in young patients, cancer cannot be a result of long-term exposure. Typical childhood cancers are known to develop as a result of strong congenital and prenatal factors. In the same way the outer circumstances of cancer genesis change with age, we also see differences in the tissue environment over the phases in life. While in early life cell division and differentiation are dominant, in adulthood, we see a period of homeostasis and maintenance with cellular repair followed by a phase of degenerative changes with apoptosis and senescence at the end of life (Rubin et al. 2010). Tumorigenesis involves the escape from these mechanisms; and consequently, we see diverse types of cancer and different response to therapy over the life span. Also, in the same way as a typical pediatric malignancy like acute lymphatic leukemia shows different genetic alterations according to pediatric age group (early age TEL-AML, later t(9;22)), it can be assumed that the genetic of adult-type cancer in children is unlike that seen in adults.

From these considerations results the interesting question, why we rarely observe adult-type tumors in childhood. Are they biologically the same tumors? Do they have the same characteristics? As cancer genesis is complex and multiple factors influence the process, the answer to these questions cannot be unilateral. We postulate that we find a combination of a genetic predisposition, immunological factors, and early exposure to environmental factors promoting cancer, which might be different from typical carcinogens of adulthood like asbestos and tobacco smoke. Anyway, there is increasing evidence that the biology and clinical characteristics of adult-type tumors in children are not the same as in adults. Several examples are given in individual disease-based chapters of this book. Here we want to give an overview of possible mechanisms.

5.3.1 Rare Typical Childhood Cancer

These are characteristic malignant tumors of childhood with generally extremely low incidence. In the phase of growth and development, mutations result in congenital defects or neoplasia. Hepatoblastoma is a typical malignant tumor of this category, arising usually in the first 2 years of life, with a mean age of onset of approximately 16–20 months (Darbari et al. 2003). The etiology is still matter of investigation; several studies suggest an interference with prenatal or postnatal exposure of the premature liver to different noxa like alcohol, oral contraceptive, and metals. Also, several genetic syndromes have been shown to be associated with hepatoblastoma: Beckwith–Wiedemann syndrome, familial adenomatous polyposis, Simpson–Golabi–Behmel syndrome, and trisomy of chromosome 8 (see Chap. 36). Interestingly, even within childhood, different phases of rapid development of organs seem to coincide with variant malignancies of these organs (Rubin et al. 2010).

5.3.2 Rare Malignancies with Different Biology in Childhood and Adulthood

Malignant tumors, which might be diagnosed both during childhood and adolescents, might be clinically and pathologically undistinguishable but biologically different, e.g., germ cell tumors in children and adults (Schneider et al. 2004). Different biological subgroups were found and defined leading to a prognostic stratification according to age in the case of mediastinal germ cell tumors (Schneider et al. 2000). Jarzab proposes that thyroid cancer in children and adults constitutes a distinct disease. He describes a different histology (more papillary thyroid cancer), a higher prevalence of rEt/Ptc rearrangements, presentation at more advanced stages, a different pattern of tumor dissemination, and higher rates of recurrence in thyroid cancer of childhood compared to adult cases (Jarzab and Handkiewicz-Junak 2007).

5.3.3 Adult-Type Cancer in Children

In adulthood, mainly carcinomas occur, probably because of the epithelium being the most active tissue and therefore prone to malignant transformation by toxins, viruses, and radiation. Long-term exposure to toxins and failure in maintenance and repair lead to oncogenesis. This is rarely the case in childhood. Etiology is likely to be different as an exposure of carcinogens over decades was not possible before the occurrence in childhood. Anyway, if we postulate that a cumulative "dose" is necessary for the development of cancer, especially intense exposure could be the explanation for early occurrence. Examples are chemotherapy/radiation therapy in case of second malignancies or the Chernobyl accident in 1986 in case of thyroid cancer (Moysich et al. 2002). For unknown reasons, the thyroid gland is more susceptible to the carcinogenetic effect of ionization in children than in adults.

Oncogenic viruses lead to cancer in all age groups but show varying importance in different countries over the world. Carcinoma of the cervix and uterus, typical malignancies of older age, appear in young women in case of exposure to herpes simplex virus type 2 and human papilloma virus. Hepatitis B and C infections are the strongest risk factors for the development of hepatocellular carcinoma in children. Consequently, in endemic areas of Southeast Asia, where hepatitis B and C infection rates are high, a high rate of hepatocellular carcinoma is seen in children (Chang et al. 1997). The utilization of hepatitis B vaccine has significantly diminished the incidence of hepatocellular carcinoma. Chronic Epstein–Barr virus infections play an important role in the malignant transformation of nasopharyngeal carcinoma cells (Raab-Traub 2002). While nasopharyngeal carcinoma is a rare malignancy in most parts of the world, it is one of the most common cancers in Southeast Asia due to specific environmental factors (certain herbs and salted fish), genetic factors, and early EBV infection (Ren et al. 2010).

For several rare tumors/adult-type tumors occurring in childhood, a genetic susceptibility or transcribed predisposition syndromes have been identified (see Chap. 6). In pediatric melanoma, etiology is not solely explained by UV exposure. Not only immunosuppression and radiotherapy have been described to play a role in carcinogenesis but also germline mutations in CDKN2A and CDK4 susceptibility genes as well as BRAF oncogene activation (Hayward 2003). Patients with Beckwith–Wiedemann syndrome, an overgrowth syndrome linked to chromosome 11p, are prone to rare (hepatoblastoma) and more frequent (Wilms' tumor and neuroblastoma) childhood tumors as well as adult-type tumors (adrenocortical carcinoma) (Clericuzio et al. 2003). A recent study found alterations in the breast cancer susceptibility genes (including BRCA 1, BRCA 2, and TP53) in 20% of women diagnosed with carcinoma of the breast under the age of 30 years (Lalloo et al. 2003). While heterozygous germline mutations in the human mismatch repair genes (MLH1, PMS2, MSH2, MSH6) predispose to the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, biallelic mutations in these genes have also been associated with occurrence of other gastrointestinal tumors in early childhood as well as childhood cancer (hematological malignancies and brain tumors) (Plaschke et al. 2006). So far, only few studies investigated the frequency of cancer susceptibility genes in early onset carcinoma.

Anyway, for some adult-type cancers, we already have a clear understanding of differing pathogenesis in children and adolescents, and therefore we can talk of *specific subentities of adult cancer types*. These are mainly cases of genetic predisposition and hereditary cancer syndromes: for example, a distinct clinicopathological entity of carcinoma of the upper aerodigestive tract showing a

balanced chromosomal translocation t(15;19), resulting in the *BRD4-NUT* fusion oncogene, was identified in young female patients. These epithelial carcinomas occur in the midline of the neck or upper thorax and are characterized by a very poor prognosis, despite aggressive multimodal treatment (Vargas et al. 2001).

5.4 Conclusion

Tumor biology and etiology change over the human life span. In consequence, clinical management cannot be transferred one-to-one from adult experience to pediatric oncology. It is crucial to learn more about the differences in biology of these tumors in order to guarantee the highest quality care for rare tumors in childhood and adolescence. Biological and epidemiological studies will have to be conducted in international cooperation in order to understand the processes underlying the differences of malignancies occurring according to age.

References

Chang MH, Chen CJ et al (1997) Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 336(26):1855–1859

Clericuzio CL, Chen E et al (2003) Serum alpha-fetoprotein screening for hepatoblastoma in children with Beckwith-Wiedemann syndrome or isolated hemihyperplasia. J Pediatr 143(2):270–272

Cotterill SJ, Ahrens S et al (2000) Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol 18(17):3108–3114

Darbari A, Sabin KM et al (2003) Epidemiology of primary hepatic malignancies in U.S. children. Hepatology 38(3): 560–566

Ferrari A, Casanova M et al (2010) Peculiar features and tailored management of adult cancers occurring in pediatric age. Expert Rev Anticancer Ther 10(11):1837–1851

Haas OA (2004) Genetic diagnosis in pediatric oncology, de Gruyter

Hayward NK (2003) Genetics of melanoma predisposition. Oncogene 22(20):3053–3062

Jarzab B, Handkiewicz-Junak D (2007) Differentiated thyroid cancer in children and adults: same or distinct disease? Hormones (Athens) 6(3):200–209

Lalloo F, Varley J et al (2003) Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 361(9363):1101–1102

Moysich KB, Menezes RJ et al (2002) Chernobyl-related ionising radiation exposure and cancer risk: an epidemiological review. Lancet Oncol 3(5):269–279

Perentesis JP (1997) Why is age such an important independent prognostic factor in acute lymphoblastic leukemia? Leukemia 11(suppl 4):S4–S7

Plaschke J, Linnebacher M et al (2006) Compound heterozygosity for two MSH6 mutations in a patient with early onset of HNPCC-associated cancers, but without hematological malignancy and brain tumor. Eur J Hum Genet 14(5): 561–566

Raab-Traub N (2002) Epstein-Barr virus in the pathogenesis of NPC. Semin Cancer Biol 12(6):431–441

Ren ZF, Liu WS et al (2010) Effect of family history of cancers and environmental factors on risk of nasopharyngeal carcinoma in Guangdong, China. Cancer Epidemiol 34(4):419–424

Rivera GK, Pui CH et al (1993) Progress in the treatment of adolescents with acute lymphoblastic leukemia. Cancer 71(10 suppl):3400–3405

Rubin P, Williams JP et al (2010) Cancer genesis across the age spectrum: associations with tissue development, maintenance, and senescence. Semin Radiat Oncol 20(1):3–11

Schneider DT, Calaminus G et al (2000) Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. J Clin Oncol 18(4):832–839

Schneider DT, Calaminus G et al (2004) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42(2):169–175

Vargas SO, French CA et al (2001) Upper respiratory tract carcinoma with chromosomal translocation 15;19: evidence for a distinct disease entity of young patients with a rapidly fatal course. Cancer 92(5):1195–1203

Genetic Predisposition and Genetic Susceptibility

6

Johannes H.M. Merks and Ines B. Brecht

Contents

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6.1 Introduction

More attention has been paid to the inherited nature of malignant tumors in children and adolescents, lately. Children with rare tumors may be at an increased risk of cancer because of a known cancer predisposition syndrome as Li-Fraumeni syndrome in case of adrenocortical tumors or multiple endocrine neoplasia (MEN2) in case of medullary thyroid tumors. Such cancer syndromes are commonly suspected in case of multiple malignancies within a family or a patient himself and/or in case of an adult-type tumor in children or adolescents. Interestingly though, it could be shown that strong predisposing mutations like BRCA1 and BRCA2, leading to individual risks of breast cancer of around 60% by age 70, together account for less than 5% of overall breast cancer incidence (Ponder 2001). Also, pediatric oncologists are not trained to pick up minor signs of cancer susceptibility, and therefore, syndromes might be overlooked. As discussed further down, it could be shown that the prevalence of minor and major morphological abnormalities is higher in patients with childhood cancers compared with controls – once more stressing the importance of constitutional genetic defects in pediatric oncogenesis and maybe pointing to so far unknown predisposition syndromes (Merks et al. 2008). This article gives an overview of mechanisms leading to cancer susceptibility, of known cancer syndromes (Table 6.1), and of the diagnostic approach and management, which can be followed in case of a suspected genetic predisposition for cancer. Within the single chapters of this book discussing the etiology of specific rare entities, several cancer syndromes are mentioned. Please refer to these chapters for detailed information on specific cancer syndromes and related malignancies.

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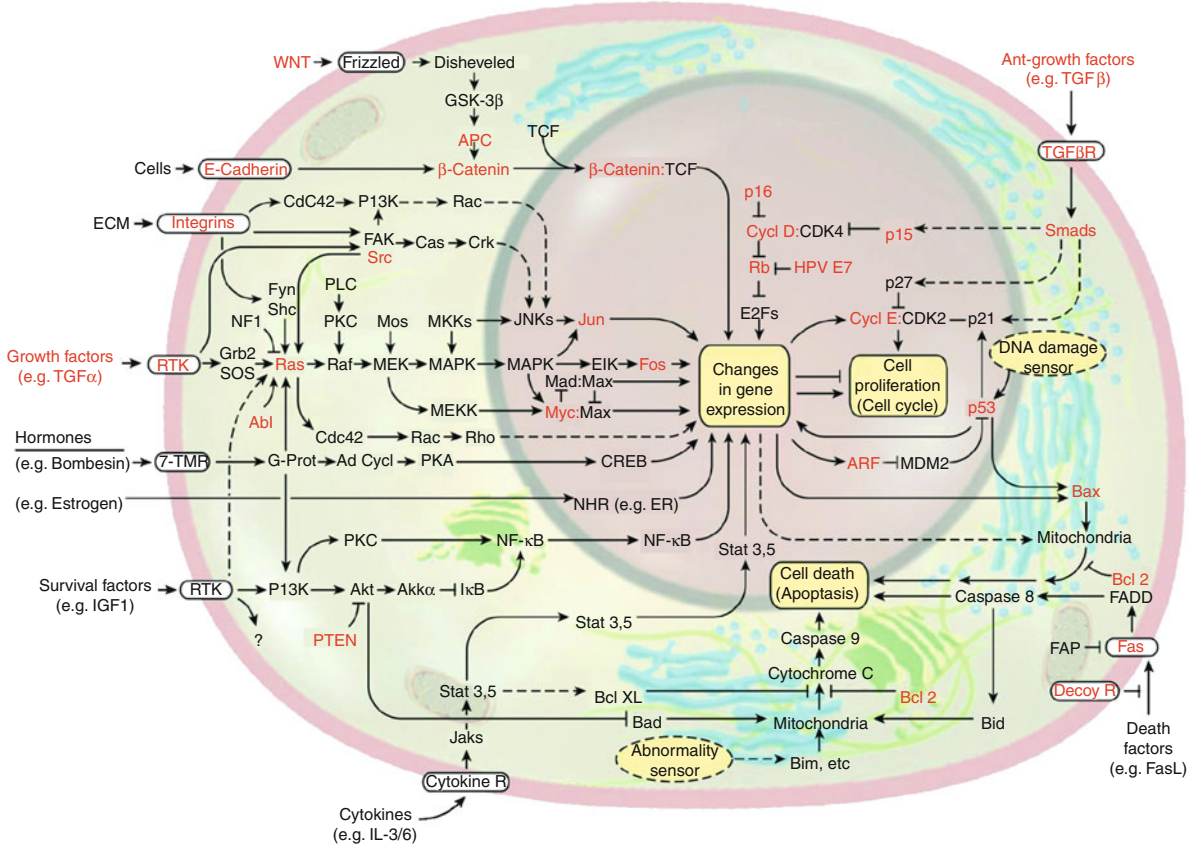

Fig. 6.1 The emergent integrated circuit of the cell (Courtesy of Hanahan and Weinberg 2000, with permission from Elsevier)

6.2 Hallmarks of Cancer Cells

Each cancer has traveled a specific route to arrive at its full phenotype. However, this multistep process can be reduced to a specific spectrum of acquired dysregulated cellular properties. Hanahan and Weinberg (2000) identified six 'hallmark characteristics' of the cancer cell phenotype:

1. *Self-sufficiency in growth signals:* Normal cells depend on mitogenic growth signals before they can enter a proliferative phase. Growth signals are transmitted to the cell via transmembrane receptors, binding three classes of signaling molecules: diffusible growth factors, extracellular matrix (ECM) components, and cell-to-cell adhesion/interaction molecules. Self-sufficiency in growth signals can be achieved by three mechanisms: (a) autocrine stimulation, i.e., cells producing their own growth factors; (b) transmembrane receptors abnormalities, such as overexpression of receptors (making the cell hyperresponsive to normal levels of growth factors), structural alterations of receptors leading to ligand independent signaling, or changes in the type of expressed ECM receptors (integrins), favoring pro-growth signals; and (c) alterations of the intracellular signaling circuit, e.g., the SOS-Ras-Raf-MAP kinase pathway playing a central role in signaling downstream of receptor tyrosine kinases (RTKs; binding diffusible growth factors) and integrins (Fig. 6.1, Hanahan and Weinberg 2000).
2. *Insensitivity to antigrowth signals:* Antigrowth signals are essential to block a cell from entering from the G1 into the S phase by inducing a quiescent (G0) state or postmitotic differentiation. Similar to growth factor signaling, antigrowth factors (soluble factors and immobilized factors embedded in the ECM) have their effect via binding to specific transmembrane receptors, inducing an intracellular signaling cascade. The intranuclear retinoblastoma protein (Rb-protein) has a central role here; in a hypophosphorylated state, Rb-protein binds to and inactivates the E2F transcription factors that control the expression of groups of genes essential for progression from G1 into S phase, blocking the cell from progression to the S phase (Weinberg 1995) (Fig. 6.1).

Normal cells are responsive to soluble antigrowth signals such as TGF-β that binds to its receptor (TGF-βR), signaling successively downstream via Smad4, p15 (INK4B), the CyclinD-CDK4 complex, eventually keeping the Rb-protein in a hypophosphorylated state (Fig. 6.1), thus blocking cell progression to a proliferative state. Disruption of the several steps of this pathway may result in insufficient response to antigrowth signals, making the cell insensitive to physiological growth inhibitory factors.

3. *Evading apoptosis:* Sensors and effectors constitute a complex circuit monitoring the intra- and extracellular environment for (ab)normalities and determining whether the cell should live or enter a phase of programmed cell death. Extracellular survival signals (e.g., IGF-1, IGF-2, and IL-3) and death signals (e.g., Fas ligand and TNFα) bind to their corresponding receptors (Fig. 6.1). Together with intracellular sensor signals, many converge on the mitochondria via different (often interacting) pathways such as the PI3–AKT pathway, members of the Bcl-2 family of proteins, and p53. When pro-apoptotic signals predominate, mitochondria release cytochrome C, catalyzing apoptosis. The ultimate effectors of apoptosis are a family of proteases, termed caspases, finally executing the death program (Fig. 6.1). Alterations in the several steps of this complex network, either potentiating the inhibitors of apoptosis (e.g., the upregulation of the Bcl-2 oncogene in lymphoma (Korsmeyer 1992)) or restraining the physiological death signals or apoptosis effectors (e.g., the epigenetic silencing of caspase 8 in neuroblastoma (Teitz et al. 2000)), withdraw the cell from its physiological "health security system."
4. *Limitless replicative potential:* Each cell seems to have a "counting device" for cell generations, called telomeres; the ends of chromosomes are composed of thousands of repeats of a short 6-base pair sequence element. Each cell replication leads to loss of 50–100 base pairs of the telomeric DNA of both ends of each chromosome. Multiple replications will lead to progressive shortening of the telomere ends, finally disabling the protective function of the telomeres after 60–70 replications (in cultured cells). This then leads to end-to-end chromosomal fusions, finally resulting in the death of the affected cell (Hayflick 1997). Telomere maintenance is a capacity virtually all cancers have obtained, either by upregulating expression of the telomerase enzyme (which adds hexanucleotide repeats onto telomeric ends) or by activating ALT, which maintains telomeres through recombination-based interchromosomal exchanges of sequence information.
5. *Sustained angiogenesis:* Like normal cells, tumor cells depend on nutrients and oxygen, obliging them to reside within 100 μm of a capillary. In a physiological state, proliferating cells are unable to induce angiogenesis. Tumor progression requires the neoplastic cells to gain angiogenic ability. Many tumors show increased expression of soluble growth factors like VEGF and FGF, both binding to their corresponding transmembrane tyrosine kinase receptors on endothelial cells. On the other hand, endogenous angiogenesis inhibitors, such as thrombospondin-1 or β-interferon, may be downregulated. Integrins and adhesion molecules, respectively mediating cell-matrix and cell-cell adhesion, play crucial roles in the regulation of angiogenesis. Proteases in the ECM can control the bioavailability of angiogenic activators and inhibitors. Disturbances at the different levels of the "angiogenic switch" may result in a sustained pro-angiogenic state.
6. *Tissue invasion and metastasis:* Cadherins, cell adhesion molecules (CAMs) (Cavallaro and Christofori 2004), integrins, and proteases (Fig. 6.1) play key roles in the ability of cancer cells to become invasive or metastatic. Normal epithelial cells show intercellular E-cadherin bridges with their neighbors, resulting in antigrowth signals via β-catenin. In most epithelial cancers this pathway is disrupted. Changes in the isoform of the cell adhesion molecule N-CAM, from a highly adhesive to a poorly adhesive or even repulsive isoform, and reductions in overall expression of the N-CAM molecule will lead to reduced cell-cell adhesion, favoring the metastatic capacity of tumor cells. Alterations of integrin expression enable the adaptation of tumor cells to a changing microenvironment in their invasive and metastatic journeys. Finally, upregulation of protease genes and downregulation of protease inhibitor genes will enable the docking of active proteases on the cancer cell surface, facilitating invasion of cancer cells into nearby structures.

6.3 Acquisition of Tumorigenic Alterations

Apparent from the six hallmarks, for a cell to become a cancer cell, multiple (epi)genetic changes have to occur to establish conflict with maintenance of

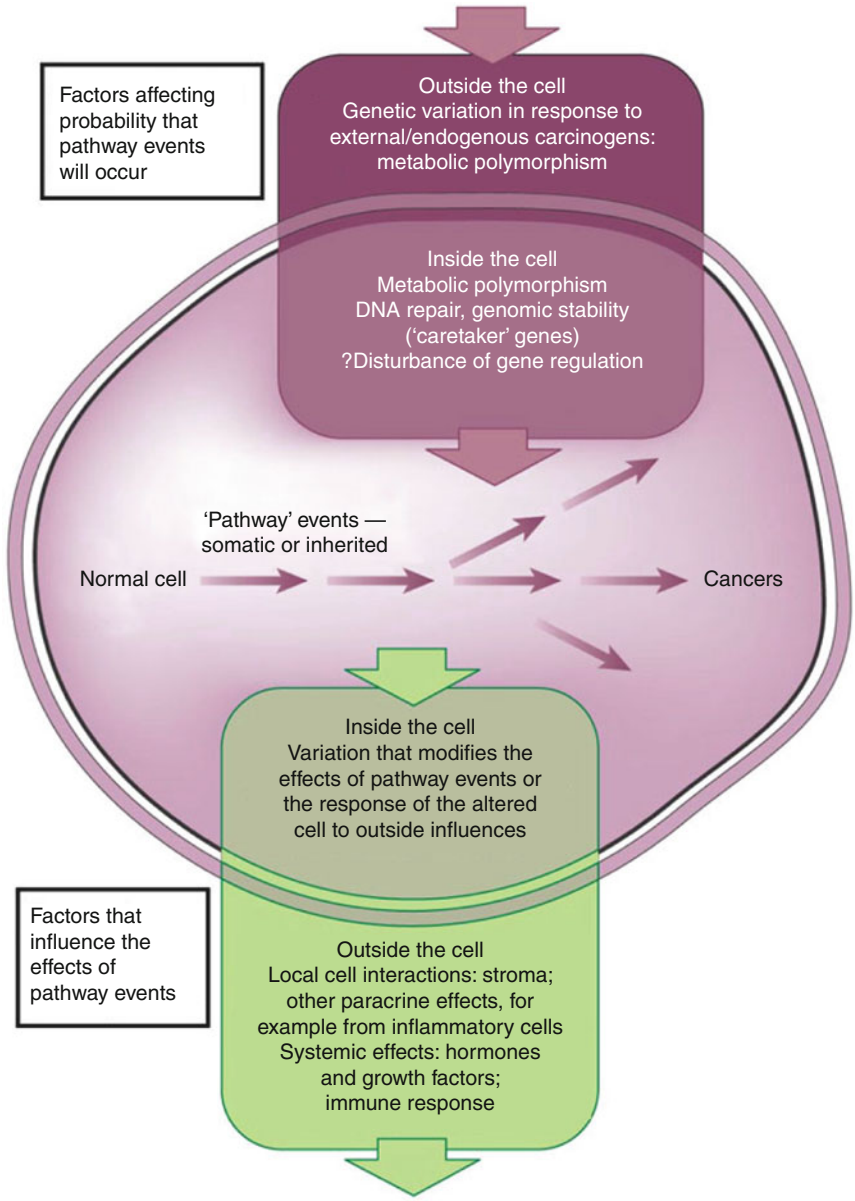

Fig. 6.2 A framework for genetic effects on cancer development (Courtesy of Bruce Ponder 2001, with permission from Nature Publishing Group). *Horizontal arrows* represent the successive pathway events giving the cell the full cancer phenotype. Many are somatic events, but in inherited cancer predisposition syndromes, one of the events is inherited. The diverging arrows on the right represent the variety of events that can lead to overtly similar cancers. *Vertical arrows* represent pathway event influencing factors

genomic integrity. Acquired or constitutive malfunction of genomic caretaker systems is often required to allow cells to take the multiple steps on the cancer ladder.

Host factors influencing the acquisition of tumorigenic alterations: The several steps in the evolution of a cancer are influenced by multiple factors from in and outside the cell (Fig. 6.2; Ponder 2001 and references therein (Ponder 2001)).

6.3.1 Factors Affecting the Probability that Tumorigenic Alterations Will Occur

External influences include environmental exposures, such as cigarette smoke, diet, or UV-light exposure, the response to which may be modified by genetic variation in intra- and extracellular metabolism (Peto 2001). For example, less than 20% of smokers develop lung cancer,

indicating that many host factors determine individual susceptibility, such as extent of carcinogen uptake, metabolic activation and detoxification, DNA repair ability, apoptosis and varying effects on genes in signal transduction pathways, and regulation of the cell cycle (Hecht 2002).

6.3.2 Factors that Influence the Effects of Tumorigenic Alterations

Variation of intracellular factors will modify the effect of a particular genetic pathway event on the cellular phenotype, or its response to signals from outside. Paracrine interactions with neighboring cells, systemic effects from circulating hormones or growth factors, and immunologic responses of the host comprise some of the external factors that modulate the effects of pathway events (Tlsty and Hein 2001; Dranoff 2004). Genetic variation of these factors probably accounts for much of the low-level predisposition to cancer, as it occurs in the "normal" population (Ponder 2001; Nadeau 2001).

6.4 Cancer Predisposition

Family history and clinical phenotype are the cardinal aspects of inherited tumor predisposition syndromes. In his review on cancer genetics, Ponder discerned strong and weak tumor predisposition (Ponder 2001). Paradoxically, the largest category of inherited tumor predisposition, in terms of its contribution to cancer incidence, is the one with the weakest genetic effects: tumor predisposition without evident family clustering, apparently caused by low-penetrance tumor predisposition genes. For example, in breast cancer, the strongly predisposing mutations in BRCA1 and BRCA2 lead to individual risks of around 60% by age 70. However, their combined contribution to overall breast cancer incidence is less than 5%. By contrast, a weak tumor predisposition gene, with a relative breast cancer risk of 2 and a population frequency of 20%, could account for up to 20% of breast cancer incidence (Ponder 2001).

Strong cancer predisposition: Strong tumor predisposition syndromes result from inheritance of either one of the events on the cancer pathway or a defective DNA repair system. Most syndromes show tissue specificity, although reasons for specific patterns of expression are mostly unclear. Another important characteristic is the variability of cancer incidence, and the type of cancers occurring within a given syndrome, but also within a single family. The within-syndrome variation can be accounted for by several factors: different germ line genes causing the same syndrome or different mutations in the same gene causing the same syndrome, genetic modifiers, environmental influences, or chance.

The within-family variation most probably is accounted for by the effects of genetic modifiers (Ponder 2001).

Weak cancer predisposition: Weak predisposition may result from weak alleles of the pathway or caretaker genes and from genetic variations of host factors influencing cancer development, as depicted in Fig. 6.2. These genes might be collectively called low-penetrance tumor predisposing genes. As described above, the word "weak" is misleading: Low-penetrance genes are thought to account for a relatively large part of cancer incidence, and studying them may provide much information about many different cancers, with important potential public health implications.

6.5 Syndromes and Childhood Cancer

Cancer syndromes account for approximately 5–10% of all cancers in adulthood. Our understanding of familial cancer syndromes is increasing rapidly, with the emphasis shifting towards early detection of at-risk families. Anyway, so far, not much is known about the exact risk of children to be affected of malignant tumors in case of a cancer syndrome, and specific prevention programs are to be established.

To establish the incidence and spectrum of malformation syndromes associated with childhood cancer, Merks et al. (2005a) performed a clinical morphological examination on a series of 1,073 children with cancer. A syndrome was diagnosed in 42 patients (3.9%) and the presence of a syndrome suspected in another 35 patients (3.3%), for a total of 7.2%. Twenty of the 42 syndrome diagnoses were not recognized in the patients prior to this study, indicating that these diagnoses are commonly missed. Therefore, all children with a malignancy should be examined by a clinical geneticist or a pediatrician skilled in clinical morphology. Besides the known syndromes, new tumor predisposition syndromes can be recognized as a result of such a meticulous clinical genetic evaluation of a large cohort of childhood cancer patients (Merks et al. 2008).

An overview of syndromes with concurring tumors in childhood is presented in Table 6.1. Most tumor syndromes in childhood are listed, together with main references and a summary of their (presumed)

Table 6.1 Childhood tumor predisposition syndromes

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Aase–Smith I (Patton et al. 1985)	AD	Unknown	Unknown	Unknown	Brain, palate, joints	Neuroblastoma	Concurrence
Acanthosis nigricans (Curth et al. 1962)	Neoplasia related	Unknown	Unknown	EpidermalGF (Douglas et al. 1994) FibroblastGF (Meyers et al. 1995)	Mouth, skin	Abdominal adenocarcinoma (60% stomach)	Tumor predisposition
Ataxia telangiectasia (Boder 1975)	AR	11q22.3	*ATM*	ATM encodes a protein similar to phosphoinositol 3-kinases, involved in mitogenic signal transduction, meiotic recombination, and cell cycle control; ATM kinase activates c-Abl tyrosine kinase in the cellular response to ionizing radiation (Baskaran et al. 1997)	Face, brain, eyes, immune system, skin	Non-Hodgkin lymphoma, acute lymphoblastic leukemia, Hodgkin disease, carcinoma (medulloblastoma, adenocarcinoma of stomach, glioma, carcinoma of skin, gallbladder, liver, larynx, thyroid, ovary, breast, and parotid gland)	Tumor predisposition
Bannayan–Riley–Ruvalcaba (Gorlin et al. 1992)	AD	10q23	*PTEN*	Tumor suppressor encoding a dual specificity phosphatase: 1. lipid phosphatase – PI3K/AKT 2. protein phosphatase – MAPK (Waite and Eng 2002)	Craniofacial, thyroid, GI-tract, musculoskeletal, skin	Lipoma, vascular malformation, hamartomas, intestinal polyposis (breast cancer, follicular thyroid cancer, endometrial carcinoma)	Tumor predisposition
Bazex–Dupré–Christol (Goeteyn et al. 1994)	X-linked dominant	Xq24-q27	Unknown	Unknown	Nose, skin	Basal cell carcinoma	Tumor predisposition
Beckwith–Wiedemann/ Wiedemann–Beckwith (Choufani et al. 2010)	Variable: cytogenetic/ gene defect/ imprinting disturbance	11p15	*IGF2, KCNQ1OT1, H19, CDKN1C*	Deregulation of imprinted genes found in 2 domains within the 11p15 region: – *IGF2* and KCNQ1OT1 (=*LIT1/KvDMR1)*: growth promoters (IGF2: autocrine growth factor; mediator of growth hormone action, stimulator of the action of insulin) – *H19* and CDKN1C (encodes the $p57^{KIP2}$ protein: tumor suppressor (Engel et al. 2000)	Overgrowth, tongue, ear, abdomen	Wilms' tumor, hepatoblastoma, adrenocortical carcinoma (hepatocellular carcinoma, neuroblastoma, glioblastoma, rhabdomyosarcoma, lymphoma, pancreaticoblastoma, renal cell carcinoma, myelodysplasia, yolk sac tumor, intratubular germ cell neoplasm, teratoma, carcinoid tumor, fibroadenoma, fibrous hamartoma, ganglioneuroma, adrenal cortex adenoma myxoma, cardiac hamartoma)	Tumor predisposition

Bloom (German 1993)	AR	15q26.1	RECQL3	Member of RecQ family helicases, maintenance of DNA integrity (Ellis and German 1996)	Growth, immune system, genitalia, skin	Acute lymphocytic leukemia, acute myeloid leukema, non-Hodgkin lymphoma, adenocarcinoma, squamous cell carcinoma (Wilms' tumor, medulloblastoma, osteosarcoma, Hodgkin lymphoma)	Tumor predisposition
Breast (and ovarian) cancer (Carter 2001)	AD	17q21 13q12.3	*BRCA1* *BRCA2*	Tumor suppressor genes; involved in maintenance of genomic integrity, at least in part by cooperating with recombinational repair proteins (Scully 2000)	Breast, ovary Breast, prostate, pancreas	(Breast cancer, ovarian cancer) (Breast cancer, pancreatic, prostate cancer)	Tumor predisposition
Carney type I (Carney 1995) Carney type II	AD 50% de novo	17q23-q24 2p16	*PRKAR1A* *Unknown*	Tumor suppressor gene, phosphorylation of many substrates including transcription factor CREB (Montminy 1997) Unknown	Eyes, heart, breast, GU-tract, endocrine system, skin	Myxomas (heart, skin, breast), pituitary tumors, adrenal cortical rest tumor, thyroid tumors, pheochromocytoma, Leydig cell tumor, large-cell calcifying Sertoli cell tumor of testis, schwannomas, myxoid breast fibroadenoma and ductal adenoma	Tumor predisposition
Cartilage-hair hypoplasia (Makitie et al. 1995)	AR	9p21-p12	RMRP	Processing of ribosomal RNA (Ridanpaa et al. 2001)	Hair, skeleton, immune system	Hodgkin disease, non-Hodgkin lymphoma, skin, eye, and liver cancer, leukemia, testicular tumor, basal cell carcinoma	Tumor predisposition
Cardio-facio-cutaneous (Armour and Allanson 2008)	sporadic	7q34 15q21 19p13.3	*BRAF, MEK1, MEK2*	*RAS/MAPK pathway*: Regulation of cell growth, differentiation, proliferation, and apoptosis *BRAF* is a proto-oncogene (Niihori et al. 2006)	Growth, craniofacial, brain, eyes, chest, heart, skin	Acute lymphoblastic leukemia, hepatoblastoma	Concurrence
Costello (Hennekam 2003)	AD	11p15.5	HRAS	Proto-oncogene; encodes signal transduction molecules (Aoki et al. 2005)	Craniofacial, brain, heart, musculoskeletal, skin	Rhabdomyosarcoma, (ganglio)neuroblastoma (bladder carcinoma, acoustic neurinoma, epithelioma)	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Cowden (Pilarski and Eng 2004)	AD	10q23	*PTEN*	Tumor suppressor encoding a dual specificity phosphatase: 1. lipid phosphatase – PI3K/AKT 2. protein phosphatase – MAPK (Waite and Eng 2002)	Craniofacial, brain, thyroid, breasts, GU-tract, GI-tract, musculoskeletal, mucocutaneous	Angiolipoma, lipoma, vascular malformations, fibroma, trichilemmoma, intestinal polyposis (breast cancer, follicular thyroid cancer, dysplastic cerebellar gangliocytoma, endometrial carcinoma, renal cell carcinoma, colon carcinoma, meningioma, medulloblastoma, parotid hamartoma, neurofibroma, granular cell tumor, salivary gland carcinoma, liopsarcoma, acute myeloid leukemia, non-Hodgkin lymphoma, melanoma, bladder carcinoma, Merkel cell carcinoma of the skin)	Tumor predisposition
Del(9p) (Huret et al. 1988)	Chromosomal	9p22 (Predeliction)	Unknown	Unknown	Craniofacial, brain, neck, chest, abdomen, limbs	Acute lymphoblastic leukemia, gonadoblastoma (in 46,XY sex reversal cases), lymphoma, melanoma	Concurrence
Del(13q) (Brown et al. 1993)	Chromosomal	13q31-13q33	Unknown	Unknown (regarding tumor predisposition: Rb tumor suppressor gene involved (Classon and Harlow 2002))	Craniofacial, brain, neck, heart, GU-tract, anus, limbs	Retinoblastoma, osteosarcoma, synovial sarcoma	Tumor predisposition
Denys–Drash (Mueller 1994)	Sporadic	11p13	WT1	Inactivation of tumor suppressor/transcription factor WT1 (Rauscher 1993)	GU-tract	Wilms' tumor (gonadoblastoma)	Tumor predisposition
Diethylstilbestrol embryopathy (Herbst et al. 1972)	Teratogen	–	–	–	GU-tract	Vaginal adenocarcinoma	Tumor predisposition
Down (Pueschel 1990)	Chromosomal	Trisomy 21	Entire chromosome 21	Overexpression of leukemogenic and solid tumor suppressor genes on chromosome 21 (Hasle et al. 2000)	Craniofacial, brain, thyroid, heart, abdomen, skeleton, skin	Acute myeloid leukemia, acute lymphoblastic leukemia *(germ cell tumor, lymphoma, retinoblastoma, pancreatic and bone tumors)*	Tumor predisposition

Dubowitz (Tsukahara and Opitz 1996)	AR	Unknown	Unknown	Unknown	Growth, craniofacial, brain, skin	Acute lymphoblastic leukemia, lymphoma, neuroblastoma , rhabdomyosarcoma, aplastic anemia	Concurrence
Dyskeratosis congenita (Sirinavin and Trowbridge 1975)	X-linked recessive	Xq28	*DKC1*	Dyskerin performs two functions: pseudouridylation and stabilization of the telomerase component of ribosomal RNA (Montanaro et al. 2006) Mutations impair telomerase maintenance, predisposing to malignancy, likely by impairing translation of tumor suppressor and antiapoptotic mRNA's	Growth, brain, eyes, ears, GI-tract, hematologic, immune system, mucocutaneous	Carcinomas of oral mucosa, nasopharynx, esophagus, stomach, rectum, cervix, and vagina; squamous cell carcinoma, adenocarcinoma of pancreas, Hodgkin disease	Tumor predisposition
Epidermal nevus/ Schimmelpenning (Goldberg et al. 1987)	Sporadic	Unknown	Unknown	Unknown	Brain, eye, skeleton, skin	Chondroblastoma, intrahepatic cyctic biliary adenomas, hemangioma, giant cell granuloma (other neoplasms may have been recorded in overlapping conditions)	Concurrence
Familial malignant melanoma (Greene 1997)	AD	9p21 12q14	*CDKN2A/p16* CDK4	Wildtype p16 arrests normal diploid cells in late G1 via inactivation of CyclinD-CDK4 complexes (Lukas et al. 1995) CyclinD-CDK4 complexes phosphorylate the Rb protein, hereby releasing the repression of E2F-mediated transcription, promoting progression through G1 (Classon and Harlow 2002)	Skin	Melanoma (pancreatic cancer) Melanoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Fanconi (Giampietro et al. 1993)	AR	16q24.3, Xp22.31, 9q22.3, 3p25.3, 6p21.3, 11p15, 9p13, 17q22-q24 2p16, 14q21.3, 13q12.3	*FANCA, FANCB, FANCC, FANCD2-FANCE, FANCF, FANCG, FANCJ, FANCL, FANCM,* FANCD1 (=biallelic BRCA2)	11 different FA genes encode for a complex web of interacting proteins that are involved in the recognition or repair of DNA interstrand crosslinks and perhaps other forms of DNA damage (Mathew 2006)	Heart, kidney, limb, hematologic, skin	Acute myeloid leukemia, myelodysplastic syndrome, hepatocellular adenoma and carcinoma, squamous cell carcinoma of head and neck, vulva and cervix medulloblastoma, Wilms' tumor, acute myeloid leukemia, acute lymphatic leukemia	Tumor predisposition
Fetal alcohol (Clarren and Smith 1978)	Teratogen	–	–	–	Growth, face, brain, heart, GU-tract, skin	(Ganglio)neuroblastoma, Wilms' tumor, germ cell tumors, hepatoblastoma, rhabdomyosarcoma, medulloblastoma, acute lymphoblastic leukemia, Hodgkin disease, adrenal carcinoma (Kiess et al. 1984)	Concurrence
Fetal hydantoin (Hanson 1986)	Teratogen	–	–	–	Growth, craniofacial, brain, neck, heart, abdomen, genitalia, limbs	Neuroblastoma, ependymoblastoma, ganglioneuroblastoma, melanotic neuroectodermal tumor of infancy, Hodgkin disease, mesenchymoma, Wilms tumor	Concurrence
Frasier (Moorthy et al. 1987)	Sporadic	11p13	WT1	Inactivation of tumor suppressor/transcription factor WT1 (Klamt et al. 1998)	GU-tract	Gonadoblastoma (Wilms')	Tumor predisposition

Gardner/familial adenomatous polyposis (Cohen 1982)	AD	5q21	*APC*	Tumor suppressor, mutations leading to stabilization of β-catenin in the WNT/β-catenin pathway, activating TCF transcription factors (Fearnhead et al. 2001)	Eyes, teeth, skeleton, GI-tract, abdomen skin	Osteoma, polyposis, colon cancer, desmoid tumors, glioma, medulloblastoma, papillary thyroid carcinoma (adrenal adenoma, adrenal adenocarcinoma, hepatocellular carcinoma, hepatoblastoma, retroperitoneal leiomyoma, neurofibroma, rhabdomyosarcoma, osteosarcoma, osteochondroma, chondrosarcoma, lipoma, fibroma of the breast, basal cell carcinoma)	Tumor predisposition
Glycogen storage disease I (Hirschhorn 2001)	AR	17q21	*G6PC*	Unknown (Limmer et al. 1988)	Growth, face, liver, kidney, musculoskeletal, skin	Liver adenomas, hepatocellular carcinomas	Tumor predisposition
Gorlin (nevoid basal cell carcinoma) (Gorlin 1987)	AD 35–50% de novo	9q22.3	*PTCH1*	Inactivation of tumor suppressor/SHH-PTCH1-SMO-GLI pathway (Villavicencio et al. 2000)	Craniofacial, brain, eyes, heart, GI-tract, ovaries, skeleton, skin	Basal cell carcinoma, medulloblastoma, cardiac fibroma, mesenteric cysts, ovarian fibroma and fibrosarcoma, rhabdomyoma, rhabdomyosarcoma, leiomyoma, leiomyosarcoma, lymphangiomyoma, melanoma, mesenchymoma, Hodgkin lymphoma, seminoma, schwannoma, pleiomorph adenoma of parotid, adrenal cortical adenoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Hemihyperplasia (Cohen 1989)	Sporadic	Unknown Partly 11p15	Unknown *IGF2, KCNQ1OT1, H19, , CDKN1C*	Unknown Deregulation of imprinted genes found in 2 domains within the 11p15 region: – IGF2 and KCNQ1OT1 (=LIT1/KvDMR1): growth promoters (IGF2: autocrine growth factor; mediator of growth hormone action, stimulator of the action of insulin) – *H19* and CDKN1C (encodes the $p57^{KIP2}$ protein: tumor suppressor (Bliek et al. 2008)	Overgrowth, face, breast, limbs	Wilms' tumor, hepatoblastoma, adrenocortical carcinoma (neuroblastoma, pheochromocytoma, testicular carcinoma, undifferentiated sarcoma)	Tumor predisposition
Hereditary leiomyomatosis and renal cell cancer (Tomlinson et al. 2002)	AD	1q42.1	*FH*	Fumarate hydratase is an enzyme of the tricarboxylic acid cycle; the mechanism leading to tumor predisposition remains unclear (Tomlinson et al. 2002)	Kidney, GU-tract, skin	(Leiomyomata of skin and uterus, renal cell carcinoma)	Tumor predisposition
Hereditary papillary renal cell carcinoma (Zbar et al. 1995)	AD	7q31	*MET*	Proto-oncogene encoding a transmembrane receptor kinase (Schmidt et al. 1997)	Kidney	(Papillary renal cell carcinoma)	Tumor predisposition
Hereditary paraganglioma and pheochromocytoma (Baysal 2002)	AD	11q23 1q21 1p36.1-p35	*SDHD* *SDHC* *SDHB*	Encoding subunits of the mitochondrial complex II; mutations possibly leading to dysregulation of hypoxia-responsive genes and impairment of mitochondria-mediated apoptosis (Maher and Eng 2002)	Adrenal glands, extra-adrenal paraganglion tissue	(Paraganglioma, pheochromocytoma)	Tumor predisposition

Hereditary non-polyposis colorectal cancer (Lynch syndrome) (Vasen et al. 1999)	AD	2p22-21 2p16 3p21 2q31-33 7p22 *Biallelic mutation carriers of:* 2p22-21 2p16 3p21 7p22	*MSH2* *MSH6* *MLH1* *PMS1* *PMS2* *MSH2* *MSH6* *MLH1* *PMS2*	DNA-mismatch repair (Lynch and de La 1999)	Breast, GI-tract, GU-tract, skin	(Colorectal and endometrial carcinoma) (Other GI and GU-tract carcinomas, skin carcinoma, breast cancer, and leukemia) Childhood primary brain malignancies, hematological malignancies, and	Tumor predisposition
Hyperparathyroidism, jaw fibroma (Inoue et al. 1995)	AD	1q25-q31	*HRPT2*	Inactivation of tumor suppressor encoding for parafibromin (Carpten et al. 2002)	Jaws, parathyroid glands	Parathyroid adenoma and carcinoma, multiple ossifying fibromas, Wilms' tumor	Tumor predisposition
Incontinentia pigmenti (Landy and Donnai 1993)	X-linked dominant	Xq28	*NEMO*	Activation of transcription factor NF-kappaB (central to many immune, inflammatory, and apoptotic pathways) (Smahi et al. 2000)	Eyes, teeth brain, skin	Retinoblastoma, Wilms' tumor, acute myeloid leukemia, rhabdomyosarcoma	Tumor predisposition
Juvenile polyposis coli (Veale et al. 1966)	AD	18q21.1 10q22.3	*SMAD4/ DPC4* *BMPR1A*	Inactivation of tumor suppressor and central mediator of Smad function in TGF-β signaling pathway (Zhang et al. 1997) Type I receptor in TGF-β/ BMP signaling (Howe et al. 2001)	GI-tract	Gastrointestinal hamartomatous polyps, GI- cancer	Tumor predisposition
Leukoplakia, tylosis, and esophageal carcinoma (Tyldesley and Hughes 1973)	AD	17q25	*EVPL*	Membrane-associated precursor of the epidermal cornified envelope, considered to link desmosomes and keratine filaments to the cornified envelope (Ruhrberg et al. 1996)	GI-tract, mucocutaneous	Leukoplakia (esophageal cancer)	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Li-Fraumeni syndrome (Li et al. 1988)	AD	17p13.1	TP53	Inactivation of tumor suppressor regulating several downstream genes: p21 and MDM-2 (cell cycle control), Gadd45 (repair) and Bax and IGF-BP (apoptosis) (Levine 1997)	Ubiquitous	Rhabdomyosarcoma, soft tissue sarcomas, brain cancer, bone sarcomas (with the exception of Ewing sarcoma), adreno-cortical tumors, leukemia, lymphoma (neuroblastoma, Wilms tumor, lung cancer, GI-cancer, endometrial cancer, squamous cell carcinoma, melanoma, breast cancer, ovary cancer, prostate cancer, thyroid cancer)	Tumor predisposition
Maffucci (Lewis and Ketcham 1973)	Sporadic	Unknown	Unknown	Unknown	Skeleton, vascular system	Vascular malformations, enchondroma, chondrosar-coma (olfactory neuroblas-toma, angiosarcoma, ovary tumors, brain tumors, pancreatic carcinoma, hepatic adenocarcinoma, pituitary adenoma)	Tumor predisposition
McCune–Albright (Danon and Crawford 1987)	Somatic mosaicism Usually sporadic	20q13.2	*GNAS1*	Activation of the stimulatory Gsα protein; Gsα protein couples receptors causing activation of adenylate cyclase, thereby increasing cAMP synthesis (Weinstein et al. 1991; Cohen and Howell 1999)	Endocrine system, skeleton, skin	Osteosarcoma, intramuscu-lar myxoma, leukemia, meningioma (breast cancer, endometrial carcinoma)	Concurrence
Mulibrey nanism (Karlberg et al. 2004)	AR	17q22-q23	*TRIM37*	Encoding a RING-B-box-coiled-coil protein of unknown function, localized in the peroxisomes (Kallijarvi et al. 2002)	Growth, face, eyes, mouth, brain, heart, liver, musculoskeletal, skin	Wilms' tumor	Tumor predisposition

Multiple endocrine neoplasia type 1 (Thakker 1998)	AD	11q13	*MEN1*	Inactivation of tumor suppressor encoding the protein menin; menin binds directly to JunD and inhibits JunD-activated transcription (Agarwal et al. 2004)	Endocrine system	(Tumors of the parathyroids, pancreatic islet cells, and anterior pituitary) (Adrenal cortical tumors, carcinoid, lipoma, angiofibroma, collagenoma)	Tumor predisposition
Multiple endocrine neoplasia type 2A (Brandi et al. 2001)	AD	10q11.2	*RET*	Proto-oncogene encoding a receptor tyrosine kinase, signaling through several pathways, including RAS/ERK, MAPK, NFκB, P13/AKT, and JNK, thus driving cell proliferation, survival, migration, or differentiation (Takahashi 2001)	Endocrine system, skin, GI-tract	Pheochromocytoma, medullary thyroid carcinoma, parathyroid adenoma	Tumor predisposition
Multiple endocrine neoplasia type 2B (Morrison and Nevin 1996)	AD 50% de novo	10q11.2	RET	See MEN 2A; 2 different MEN 2B specific mutations: 96% M918T 4% A883F (Eng et al. 1996)	Face, eyes, larynx, thyroid, adrenal gland, GI-tract, musculoskeletal	Pheochromocytoma, medullary thyroid carcinoma, mucosal neuroma	Tumor predisposition
Neurofibromatosis type I (Viskochil 1999)	AD 50% de novo	17q11.2	*NF1*	Inactivation of tumor suppressor/loss of inhibition of Ras oncogene activity (Cichowski and Jacks 2001)	Craniofacial, eyes, brain, vascular system, skeleton, skin	Neurofibroma, plexiform neurofibroma, optic glioma, schwannoma, meningioma, astrocytoma, medulloblastoma, ependymoma, neurofibrosarcoma, malignant peripheral nerve sheath tumor (rhabdomyosarcoma, neuroblastoma, Wilms tumor, juvenile myelomonocytic leukemia, pheochromocytoma, adenosarcoma of pancreas, liposarcoma, melanoma)	Tumor predisposition
Neurofibromatosis type II (Evans et al. 2000)	AD	22q12.2	*NF2*	Inactivation of tumor suppressor/loss of merlin interaction with multiple proteins involved in cell-cell and cell-matrix signals (Gutmann 2001)	Eyes, brain, skin	Acoustic neuroma, neurofibroma, meningioma, glioma, schwannoma, ependymoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Nijmegen breakage (van der Burgt et al. 1996)	AR	8q21	*NBS1*	Mutated DNA double-strand break repair protein; Nbs1 potentiates ATP-driven DNA unwinding and endonuclease cleavage by the Mre11/Rad50 complex (Varon et al. 1998; Paull and Gellert 1999)	Growth, craniofacial, immune system	Acute lymphoblastic leukemia, lymphoma, neuroblastoma, glioma, medulloblastoma, rhabdomyosarcoma	Tumor predisposition
Noonan (Allanson 1987)	AD 25–70% de novo	12q24.1	*PTPN11*	Gain of function in tyrosine phosphatase SHP2. SHP2 is involved in intracellular signaling downstream to several growth factor, cytokine, and hormone receptors. SHP2 stimulates the RAS/MAPK pathway (Fragale et al. 2004)	Growth, craniofacial, eyes, brain, heart, lymphatic system, abdomen, GU-tract, skeleton, skin	Juvenile myelomonocytic leukemia, neuroblastoma (acute lymphoblastic leukemia, chronic myelomonocytic leukemia, rhabdomyosarcoma, testicular carcinoma, pheochromocytoma, astrocytoma, hepatoblastoma, malignant peripheral nerve sheath tumor)	Tumor predisposition
Opitz trigonocephaly (Antley et al. 1981)	Uncertain	Unknown	Unknown	Unknown	Craniofacial, brain, neck, heart, genital, limbs, skin	(Medulloblastoma)	Concurrence
Peutz–Jeghers (Westerman et al. 1999)	AD	19p13.3	*STK11*	Inactivation of tumor suppressor gene by loss of protein kinase activity; *STK11* interacts with the chromatin remodeling protein BRG1 and with the cell cycle regulatory proteins LIP1 and WAF1 (Yoo et al. 2002)	GI-tract, GU-tract, mucocutaneous	Gastointestinal hamartomas, adenomas and adenocarcinomas, granulosa cell tumors, dysgerminoma, cystadenoma, cervical adenocarcinoma, sex cord tumor with annular tubules, large cell Sertoli cell tumor, breast carcinoma, pancreatic adenocarcinoma, bile duct carcinoma	Tumor predisposition
Proteus (Biesecker et al. 1999)	Somatic mosaicism	Up to 20% of cases: 10q23 (Zhou et al. 2001)	Up to 20% of cases: *PTEN*	Inactivation of tumor suppressor encoding a dual specificity phosphatase: 1. lipid phosphatase – PI3K/AKT 2. protein phosphatase – MAPK (Waite and Eng 2002)	Overgrowth, craniofacial, lung, kidney, vascular system, skeleton, skin	Vascular malformations, lipomas (ovarian cystadenoma, testicular tumors, meningiomas, monomorphic adenoma of parotid gland)	Tumor predisposition
		Remainder: 14q32.33	Remainder: AKT1				
	(Lindhurst et al. 2011)			Mosaic activation of AKT1 (Lindhurst et al. 2011)			

Retinoblastoma (hereditary) (Knudson et al. 1975)	AD 80% de novo	13q14.1-q14.2	*RB1*	Inactivation of tumor suppressor/repressor of E2F-mediated transcription, inhibiting progression through G1 (Classon and Harlow 2002)	Eyes	Retinoblastoma, osteosarcoma, pinealoma	Tumor predisposition
Ring-shaped skin creases, cleft palate (Cohen et al. 1993)	AD	Unknown	Unknown	Unknown	Craniofacial, skin	Neuroblastoma, smooth muscle hamartoma	Concurrence
Rothmund–Thomson (Wang et al. 2001a)	AR	8q24.3	*RECQL4*	Member of RecQ family helicases; maintenance of DNA integrity (Kitao et al. 1999)	Growth, craniofacial, eyes, endocrine system, limbs, skeleton, skin	Osteosarcoma, fibrosarcoma, squamous cell carcinoma (melanoma, gastric carcinoma)	Tumor predisposition
Rubinstein–Taybi (Rubinstein 1990)	AD >99% de novo	16p13.3	*CBP*	Haploinsufficiency of the transcriptional cofactor CBP, which is involved as downstream effector in many pathways, particularly the SHH-PTCH-GLI pathway (Petrij et al. 1995)	Growth, craniofacial, brain, GU-tract, limbs, skeleton	Rhabdomyosarcoma, neuroblastoma, pheochromocytoma, acute lymphoblastic leukemia, angioblastic meningioma, neurilemmoma, gonadal sex cord stromal cell tumor, hemangioendothelioma, acute leukemia	Tumor predisposition
Silver–Russell (Patton 1988)	Heterogeneous	Heterogeneous 11p15.5 Maternal disomy 7	*IGF2, H19*	Deregulation of imprinted genes found in 2 domains within the 11p15 region: – *IGF2* autocrine growth factor; mediator of growth hormone action, stimulator of the action of insulin (Binder et al. 2006) – *H19*: tumor suppressor (Bliek et al. 2006)	Growth, face, GU-tract, musculoskeletal, limbs, skin	Gonadoblastoma, testicular seminoma, hepatocellular carcinoma, craniopharyngioma, astrocytoma,	Concurrence
Simpson–Golabi–Behmel (Neri et al. 1998)	X-linked recessive	Xq26	*GPC3*	Cell surface heparan sulfate proteoglycan, binding to IGF2 and modulating IGF2 action (DeBaun et al. 2001)	Growth, craniofacial, brain, heart, musculoskeletal, limbs, skin	Wilms' tumor, atypical embryoma, neuroblastoma, hepatoblastoma, rhabdomyoma, hepatocellular carcinoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Sotos (cerebral gigantism) (Cole and Hughes 1994)	AD	5q35	NSD1	Co-regulation of transcription via interaction with steroid receptors (Wang et al. 2001b)	Growth, craniofacial, brain	Wilms' tumor, hepatocellular carcinoma, neuroblastoma, sacrococcygeal teratoma, acute lymphoblastic leukemia, lymphoma, giant cell granuloma of mandible (vaginal epidermoid carcinoma, small cell lung carcinoma)	Tumor predisposition
Trisomy 8 (Riccardi 1977)	Chromosomal	Trisomy 8	Entire chromosome 8	Unknown	Growth, craniofacial, brain, heart, GU-tract, skeleton, limbs	Wilms' tumor, leukemia	Concurrence
Trisomy 13 (Wyllie et al. 1994)	Chromosomal	Trisomy 13	Entire chromosome 13	Unknown	Growth, craniofacial, brain, neck, heart, genitalia, limbs, skin	Wilms' tumor, leukemia, neuroblastoma	Concurrence
Trisomy 18 (Baty et al. 1994)	Chromosomal	Trisomy 18	Entire chromosome 18	Unknown	Growth, craniofacial, brain, neck, heart, GU-tract, skeleton, limbs	Wilms' tumor, hepatoblastoma, neurogenic tumor	Concurrence
Tuberous sclerosis (Gomez 1991)	AD 66% de novo	9q34 16p13.3	*TSC1* *TSC2*	Inactivation of tumor suppressors tuberin and hamartin that normally inactivate the phosphatidylinositol-3 kinase (PI3K)–AKT–mTOR–S6K pathway leading to cell size increase and growth (Kwiatkowski 2003)	Brain, heart, kidney, skeleton, skin	Tubers, astrocytoma, rhabdomyoma, fibroma, angiofibroma, hemangioma of the spleen, retinal hamartoma, renal and hepatic angiomyolipomas, renal cell carcinoma, pulmonary lymphangiomyomatosis	Tumor predisposition
Turcot (Itoh et al. 1993)	AD AD AR	5q21-q22 3p21.3 7p22	*APC* *MLH1* *Biallelic mutations in PMSL2*	Tumor suppressor, mutations leading to stabilization of β-catenin in the WNT/β-catenin pathway, activating TCF transcription factors (Fearnhead et al. 2001) DNA nucleotide mismatch repair (Hemminki et al. 1994) *DNA nucleotide mismatch repair* (Nicolaides et al. 1994; Felton et al. 2007)	Brain, GI-tract	Polyposis, colon cancer, medulloblastoma, supratentorial primitive neuroectodermal tumor, glioblastoma, ependymoma, astrocytoma, oligodendroglioma, neuroblastoma, non-Hodgkin lymphoma, acute lymphoblastic leukemia	Tumor predisposition

Turner (Hall and Gilchrist 1990)	Chromosomal	X0	Entire X chromosome missing	Unknown	Growth, craniofacial, neck, chest, heart, immune system, GU-tract, skeleton, skin	Gonadoblastoma (dysgerminoma, (ganglio) neuroblastoma, schwannoma, mesenchymoma, acute myeloid leukemia, medulloblastoma, pituitary adenoma,glioma, meningioma, ,melanoma, hibernoma, thyroid carcinoma, anaplastic lung tumor, adenocarcinoma of uterus and GI tract, squamous cell carcinoma of vulva)	Tumor predisposition
Tyrosinemia type I (Kvittingen 1991)	AR	15q23-q25	*FAH*	Fumarylacetoacetate induces spindle disturbances and segregational defects (Jorquera and Tanguay 2001)	Liver, kidney, musculoskeletal	Hepatocellular carcinoma	Tumor predisposition
Unusual face, osteosarcoma, and malformation (Schuman and Burton 1979)	Uncertain	Unknown	Unknown	Unknown	Craniofacial, GU-tract	Osteosarcoma	Tumor predisposition
Von Hippel–Lindau (Lonser et al. 2003)	AD	3p25-26	*VHL*	Tumor suppressor gene; induces degradation of HIF. HIF coordinates the cell response to hypoxia by increasing expression of angiogenic, growth, and mitogenic factors including VEGF, PDGFβ, erythropoietin, and TGFα (Kaelin 2002)	Central nervous system, abdomen, GU-tract	Retinal and central nervous system hemangioblastoma, renal cell carcinoma, pancreatic tumors, pheochromocytoma	Tumor predisposition
WAGR (Wilms' tumor, aniridia, genitourinary malformations, retardation) (Riccardi et al. 1978)	Sporadic	11p13 (contiguous gene defect, including WT1 and PAX6)	*WT1* *PAX6*	Inactivation of tumor suppressor/transcription factor WT1 (Little and Wells 1997) Role in oculogenesis (Wawersik and Maas 2000)	Eyes, brain, heart, GU-tract, vertebrae	Wilms' tumor	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Werner (Goto et al. 1981)	AR	8p12-p11.2	*WRN*	Member of RecQ family helicases; maintenance of genome integrity (Mohaghegh and Hickson 2001)	Face, brain, endocrine system, vascular system, musculoskeletal, skin	Meningioma, paraganglioma, adenoma of the pituitary gland, thyroid and adrenal gland; basal and squamous cell carcinoma and melanoma, adenocarcinoma of thyroid, stomach, ovary, and liver, fibrosarcoma, neurofibrosarcoma, leiomyosarcoma, and osteosarcoma	Tumor predisposition
Xeroderma pigmentosum (Cohen and Levy 1989)	AR	9q22.3 2q21 3p25 19q13.2-q13.3 11p12-p11 16p13.3-p13.13 13q33	*XPA-XPG*	XP proteins are part of the nucleotide excision repair complex (Friedberg 2001)	Face, eyes, oral, brain, skin	Basal cell carcinoma, squamous cell carcinoma, melanoma, fibrosarcoma, angiosarcoma, fibroma, angioma	Tumor predisposition
47 XXY (Caldwell and Smith 1972)	Chromosomal	Extra X chromosome	–	–	Growth, craniofacial, brain, genital	Breast cancer, seminoma of testis (lymphoma, leukemia, germinoma)	Tumor predisposition

Syndromes with reported tumor incidence in childhood are listed. For each syndrome, the following items are mentioned: mode of inheritance, involved locus, responsible gene(s), (presumed) pathogenic pathway, body regions involved, and co-occurring tumors. Relatively uncommon tumors in the syndrome or in childhood are in brackets. The association of a syndrome with malignancy is given as "tumor predisposition" or "concurrence," the latter meaning that there might be an association, but data are insufficient to draw definitive conclusion

AD autosomal dominant, *AR* autosomal recessive, *GI* gastrointestinal, *GU* genitourinary

pathogenic pathway. The role of metabolic defects in cancer development and pediatric syndromes appears to be of growing importance; a few well-known examples are listed too. For details on gastrointestinal cancer predisposition syndromes refer to Chap. 30.

In recent years, it has become apparent that biallelic mutation carriers of autosomal dominant adult cancer syndromes are at a very high risk of developing specific childhood cancers often at a very young age (Rahman and Scott 2007). Biallelic mutations of BRCA2 lead to the autosomal recessive childhood cancer syndrome Fanconi anemia D1. Biallelic mutations in the mismatch repair deficiency genes MSH2, MLH1, MSH6, and PMS2 lead to a mismatch-repair-deficiency syndrome with childhood malignancies occurring at a very young age, while monoallelic mutation carriers develop hereditary nonpolyposis colorectal cancer.

6.6 Diagnostic Approach and Management in Case of Suspected Genetic Predisposition

Hereditary malignant tumors tend to occur in an earlier stage of life than the same tumor occurring sporadically. It is difficult to decide when an inherited cancer predisposition should be considered. One should suspect the presence of a tumor predisposition syndrome in case:

- An increased number of family members are diagnosed with cancer, e.g., two or more close relatives have had the same type of malignancy or two and more siblings develop a malignancy.
- A malignant tumor is diagnosed at an unusual early stage of life.
- Clustering of malignant tumors related to a known cancer syndrome is seen within a family (e.g., NCCN guidelines, link: http://www.nccn.org/index.asp).
- Clustering of rare malignant tumors (e.g., sarcomas) within a family is seen (see Table 6.1 for associated syndromes).
- More than one primary cancer is diagnosed within the patient.
- Of the presence of precursor lesions or specific benign tumors, e.g., adenomatous polyps in case of familial adenomatous polyposis, atypical, dysplastic nevi of the skin in case of hereditary melanoma, or lipomas in case of multiple endocrine neoplasia type 1.

A family tree from each side of the family should be constructed. It should include specific information on cancer types, syndromes, and other health conditions possibly related to certain malignancies. Generally speaking, the closer the relationship to the patient, the more detailed information is needed. As most familial cancer syndromes are inherited autosomal dominant, malignant tumors are found in successive generations.

In addition to the family history, the clinical examination is an essential part of a screening exam for cancer predisposition. As discussed above, half of tumor predisposition syndromes are missed by pediatric oncologists (Merks et al. 2005). Therefore, we strongly feel that all children with a malignancy should be examined by a clinical geneticist or a pediatrician skilled in clinical morphology in order to evaluate for morphological abnormalities. Internet databases and handbooks can help classifying and interpreting morphological abnormalities (Jones 2006; Winter and Baraitser 2009; Sijmons http://www.facd.info). However, those databases work best for clinical geneticists trained in this field.

After all, it is important to be aware of a possible underlying genetic predisposition in any case of rare pediatric tumor. In fact, many pediatric cancers are very rare diseases in itself, and therefore every child deserves a clinical genetic examination once in the course of its disease.

6.6.1 Management in Case of Cancer Predisposition

Familial cancer syndromes and most associated malignant tumors are extremely rare in children. Therefore, it is important to get help from physicians who are expert in the field of these rare entities, and a multidisciplinary approach has to be coordinated. Patients with genetic predisposition to cancer may have other diseases and conditions (such as endocrine disorders and immune defects) which make a comprehensive approach crucial.

Ideally, a personalized plan in order to reduce the risk of a malignancy should be developed for the patient and/or family members. This plan may include:

- Annual physical exams with additional examinations depending on the specific rare tumors that have occurred in the family
- Evaluation of any symptoms, even though they may resemble common diseases, that have persisted for

several weeks, such as abdominal pain, bone pain, growths, headaches, etc.
- Education and awareness of the signs and symptoms of cancer
- Recommendations for changes in lifestyle, such as diet, exercise, and other factors
- Genetic testing
- Participation in clinical trials to prevent and detect cancer
- Psychological support

Although genetic testing is available for many familial cancer syndromes, there are genes that have yet to be discovered. Although many hospitals in the US have a "familial cancer clinic," which is a team of health professionals with expertise in familial cancer syndromes, this is still not the case in most countries. In general, geneticists, oncologists, and social workers have to work together in order to assist individuals and families by providing risk assessment, support, screening and prevention recommendations, and genetic testing options.

References

Agarwal SK, Lee BA, Sukhodolets KE, Kennedy PA, Obungu VH, Hickman AB, Mullendore ME, Whitten I, Skarulis MC, Simonds WF, Mateo C, Crabtree JS, Scacheri PC, Ji Y, Novotny EA, Garrett-Beal L, Ward JM, Libutti SK, Richard AH, Cerrato A, Parisi MJ, Santa A, Oliver B, Chandrasekharappa SC, Collins FS, Spiegel AM, Marx SJ (2004) Molecular pathology of the MEN1 gene. Ann N Y Acad Sci 1014:189–198

Allanson JE (1987) Noonan syndrome. J Med Genet 24(1): 9–13

Antley RM, Hwang DS, Theopold W, Gorlin RJ, Steeper T, Pitt D, Danks DM, McPherson E, Bartels H, Wiedemann HR, Opitz JM (1981) Further delineation of the C (trigonocephaly) syndrome. Am J Med Genet 9(2):147–163

Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, Filocamo M, Kato K, Suzuki Y, Kure S, Matsubara Y (2005) Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet 37(10):1038–1040

Armour CM, Allanson JE (2008) Further delineation of cardio-facio-cutaneous syndrome: clinical features of 38 individuals with proven mutations. J Med Genet 45(4): 249–254

Baskaran R, Wood LD, Whitaker LL, Canman CE, Morgan SE, Xu Y, Barlow C, Baltimore D, Wynshaw-Boris A, Kastan MB, Wang JY (1997) Ataxia telangiectasia mutant protein activates c-Abl tyrosine kinase in response to ionizing radiation. Nature 387(6632):516–519

Baty BJ, Blackburn BL, Carey JC (1994) Natural history of trisomy 18 and trisomy 13: I. Growth, physical assessment, medical histories, survival, and recurrence risk. Am J Med Genet 49(2):175–188

Baysal BE (2002) Hereditary paraganglioma targets diverse paraganglia. J Med Genet 39(9):617–622

Biesecker LG, Happle R, Mulliken JB, Weksberg R, Graham JM Jr, Viljoen DL, Cohen MM Jr (1999) Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. Am J Med Genet 84(5):389–395

Binder G, Seidel AK, Weber K, Haase M, Wollmann HA, Ranke MB, Eggermann T (2006) IGF-II serum levels are normal in children with Silver-Russell syndrome who frequently carry epimutations at the IGF2 locus. J Clin Endocrinol Metab 91(11):4709–4712

Bliek J, Terhal P, van den Bogaard MJ, Maas S, Hamel B, Salieb-Beugelaar G, Simon M, Letteboer T, van der Smagt J, Kroes H, Mannens M (2006) Hypomethylation of the H19 gene causes not only Silver-Russell syndrome (SRS) but also isolated asymmetry or an SRS-like phenotype. Am J Hum Genet 78(4):604–614

Bliek J, Maas S, Alders M, Merks JH, Mannens M (2008) Epigenotype, phenotype, and tumors in patients with isolated hemihyperplasia. J Pediatr 153(1):95–100

Boder E (1975) Ataxia-telangiectasia: some historic, clinical and pathologic observations. Birth Defects Orig Artic Ser 11(1):255–270

Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr, Marx SJ (2001) Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 86(12):5658–5671

Brown S, Gersen S, Anyane-Yeboa K, Warburton D (1993) Preliminary definition of a "critical region" of chromosome 13 in q32: report of 14 cases with 13q deletions and review of the literature. Am J Med Genet 45(1):52–59

Caldwell PD, Smith DW (1972) The XXY (Klinefelter's) syndrome in childhood: detection and treatment. J Pediatr 80(2):250–258

Carney JA (1995) Carney complex: the complex of myxomas, spotty pigmentation, endocrine overactivity, and schwannomas. Semin Dermatol 14(2):90–98

Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, Simonds WF, Gillanders EM, Kennedy AM, Chen JD, Agarwal SK, Sood R, Jones MP, Moses TY, Haven C, Petillo D, Leotlela PD, Harding B, Cameron D, Pannett AA, Hoog A, Heath H III, James-Newton LA, Robinson B, Zarbo RJ, Cavaco BM, Wassif W, Perrier ND, Rosen IB, Kristoffersson U, Turnpenny PD, Farnebo LO, Besser GM, Jackson CE, Morreau H, Trent JM, Thakker RV, Marx SJ, Teh BT, Larsson C, Hobbs MR (2002) HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet 32(4):676–680

Carter RF (2001) BRCA1, BRCA2 and breast cancer: a concise clinical review. Clin Invest Med 24(3):147–157

Cavallaro U, Christofori G (2004) Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. Nat Rev Cancer 4(2):118–132

Choufani S, Shuman C, Weksberg R (2010) Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet 154C(3): 343–354

Cichowski K, Jacks T (2001) NF1 tumor suppressor gene function: narrowing the GAP. Cell 104(4):593–604

Clarren SK, Smith DW (1978) The fetal alcohol syndrome. N Engl J Med 298(19):1063–1067
Classon M, Harlow E (2002) The retinoblastoma tumour suppressor in development and cancer. Nat Rev Cancer 2(12):910–917
Cohen SB (1982) Familial polyposis coli and its extracolonic manifestations. J Med Genet 19(3):193–203
Cohen MM Jr (1989) A comprehensive and critical assessment of overgrowth and overgrowth syndromes. Adv Hum Genet 18:181–186
Cohen MM Jr, Howell RE (1999) Etiology of fibrous dysplasia and McCune-Albright syndrome. Int J Oral Maxillofac Surg 28(5):366–371
Cohen MM, Levy HP (1989) Chromosome instability syndromes. Adv Hum Genet 18:43–71
Cohen MM Jr, Gorlin RJ, Clark R, Ewing SG, Camfield PR (1993) Multiple circumferential skin folds and other anomalies: a problem in syndrome delineation. Clin Dysmorphol 2(1):39–46
Cole TR, Hughes HE (1994) Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet 31(1): 20–32
Curth HO, Hilberg AW, Machacek GF (1962) The site and histology of the cancer associated with malignant acanthosis nigricans. Cancer 15:364–382
Danon M, Crawford JD (1987) The McCune-Albright syndrome. Ergeb Inn Med Kinderheilkd 55:81–115
DeBaun MR, Ess J, Saunders S (2001) Simpson Golabi Behmel syndrome: progress toward understanding the molecular basis for overgrowth, malformation, and cancer predisposition. Mol Genet Metab 72(4):279–286
Douglas F, McHenry PM, Dagg JH, MacBeth FM, Morley WN (1994) Elevated levels of epidermal growth factor in a patient with tripe palms. Br J Dermatol 130(5):686–687
Dranoff G (2004) Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer 4(1):11–22
Ellis NA, German J (1996) Molecular genetics of Bloom's syndrome. Hum Mol Genet 5 Spec No:1457–1463
Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, van Amstel HK, Lips CJ, Nishisho I, Takai SI, Marsh DJ, Robinson BG, Frank-Raue K, Raue F, Xue F, Noll WW, Romei C, Pacini F, Fink M, Niederle B, Zedenius J, Nordenskjold M, Komminoth P, Hendy GN, Mulligan LM (1996) The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. JAMA 276(19):1575–1579
Engel JR, Smallwood A, Harper A, Higgins MJ, Oshimura M, Reik W, Schofield PN, Maher ER (2000) Epigenotype-phenotype correlations in Beckwith-Wiedemann syndrome. J Med Genet 37(12):921–926
Evans DG, Sainio M, Baser ME (2000) Neurofibromatosis type 2. J Med Genet 37(12):897–904
Fearnhead NS, Britton MP, Bodmer WF (2001) The ABC of APC. Hum Mol Genet 10(7):721–733
Felton KE, Gilchrist DM, Andrew SE (2007) Constitutive deficiency in DNA mismatch repair. Clin Genet 71(6):483–498
Fragale A, Tartaglia M, Wu J, Gelb BD (2004) Noonan syndrome-associated SHP2/PTPN11 mutants cause EGF-dependent prolonged GAB1 binding and sustained ERK2/MAPK1 activation. Hum Mutat 23(3):267–277
Friedberg EC (2001) How nucleotide excision repair protects against cancer. Nat Rev Cancer 1(1):22–33
German J (1993) Bloom syndrome: a mendelian prototype of somatic mutational disease. Medicine (Baltimore) 72(6):393–406
Giampietro PF, Adler-Brecher B, Verlander PC, Pavlakis SG, Davis JG, Auerbach AD (1993) The need for more accurate and timely diagnosis in Fanconi anemia: a report from the International Fanconi Anemia Registry. Pediatrics 91(6):1116–1120
Goeteyn M, Geerts ML, Kint A, De Weert J (1994) The Bazex-Dupre-Christol syndrome. Arch Dermatol 130(3):337–342
Goldberg LH, Collins SA, Siegel DM (1987) The epidermal nevus syndrome: case report and review. Pediatr Dermatol 4(1):27–33
Gomez MR (ed) (1991) Tuberous Sclerosis and Allied Disorders: Clinical, Cellular, and Molecular Studies, vol 165. New York Academy of Science, New York
Gorlin RJ (1987) Nevoid basal-cell carcinoma syndrome. Medicine (Baltimore) 66(2):98–113
Gorlin RJ, Cohen MM Jr, Condon LM, Burke BA (1992) Bannayan-Riley-Ruvalcaba syndrome. Am J Med Genet 44(3):307–314
Goto M, Tanimoto K, Horiuchi Y, Sasazuki T (1981) Family analysis of Werner's syndrome: a survey of 42 Japanese families with a review of the literature. Clin Genet 19(1): 8–15
Greene MH (1997) Genetics of cutaneous melanoma and nevi. Mayo Clin Proc 72(5):467–474
Gutmann DH (2001) The neurofibromatoses: when less is more. Hum Mol Genet 10(7):747–755
Hall JG, Gilchrist DM (1990) Turner syndrome and its variants. Pediatr Clin North Am 37(6):1421–1440
Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57–70
Hanson JW (1986) Teratogen update: fetal hydantoin effects. Teratology 33(3):349–353
Hasle H, Clemmensen IH, Mikkelsen M (2000) Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 355(9199):165–169
Hayflick L (1997) Mortality and immortality at the cellular level. A review. Biochemistry (Mosc) 62(11):1180–1190
Hecht SS (2002) Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. Lancet Oncol 3(8):461–469
Hemminki A, Peltomaki P, Mecklin JP, Jarvinen H, Salovaara R, Nystrom-Lahti M, de La CA, Aaltonen LA (1994) Loss of the wild type MLH1 gene is a feature of hereditary nonpolyposis colorectal cancer. Nat Genet 8(4):405–410
Hennekam RC (2003) Costello syndrome: an overview. Am J Med Genet 117C(1):42–48
Herbst AL, Kurman RJ, Scully RE (1972) Vaginal and cervical abnormalities after exposure to stilbestrol in utero. Obstet Gynecol 40(3):287–298
Hirschhorn R (2001) Glycogen storage disease type I. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular basis of inherited disease, 8th edn. McGraw-Hill, New York, pp 1530–1535
Howe JR, Bair JL, Sayed MG, Anderson ME, Mitros FA, Petersen GM, Velculescu VE, Traverso G, Vogelstein B (2001) Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. Nat Genet 28(2):184–187

Huret JL, Leonard C, Forestier B, Rethore MO, Lejeune J (1988) Eleven new cases of del(9p) and features from 80 cases. J Med Genet 25(11):741–749

Inoue H, Miki H, Oshimo K, Tanaka K, Monden Y, Yamamoto A, Kagawa S, Sano N, Hayashi E, Nagayama M (1995) Familial hyperparathyroidism associated with jaw fibroma: case report and literature review. Clin Endocrinol (Oxf) 43(2):225–229

Itoh H, Hirata K, Ohsato K (1993) Turcot's syndrome and familial adenomatous polyposis associated with brain tumor: review of related literature. Int J Colorectal Dis 8(2):87–94

Jones KL (2006) Smith's Recognizable patterns of human malformation, 6th edn. Elsevier Saunders, Philadelphia

Jorquera R, Tanguay RM (2001) Fumarylacetoacetate, the metabolite accumulating in hereditary tyrosinemia, activates the ERK pathway and induces mitotic abnormalities and genomic instability. Hum Mol Genet 10(17):1741–1752

Kaelin WG Jr (2002) Molecular basis of the VHL hereditary cancer syndrome. Nat Rev Cancer 2(9):673–682

Kallijarvi J, Avela K, Lipsanen-Nyman M, Ulmanen I, Lehesjoki AE (2002) The TRIM37 gene encodes a peroxisomal RING-B-box-coiled-coil protein: classification of mulibrey nanism as a new peroxisomal disorder. Am J Hum Genet 70(5): 1215–1228

Karlberg N, Jalanko H, Perheentupa J, Lipsanen-Nyman M (2004) Mulibrey nanism: clinical features and diagnostic criteria. J Med Genet 41(2):92–98

Kiess W, Linderkamp O, Hadorn HB, Haas R (1984) Fetal alcohol syndrome and malignant disease. Eur J Pediatr 143(2):160–161

Kitao S, Shimamoto A, Goto M, Miller RW, Smithson WA, Lindor NM, Furuichi Y (1999) Mutations in RECQL4 cause a subset of cases of Rothmund-Thomson syndrome. Nat Genet 22(1):82–84

Klamt B, Koziell A, Poulat F, Wieacker P, Scambler P, Berta P, Gessler M (1998) Frasier syndrome is caused by defective alternative splicing of WT1 leading to an altered ratio of WT1 +/−KTS splice isoforms. Hum Mol Genet 7(4):709–714

Knudson AG Jr, Hethcote HW, Brown BW (1975) Mutation and childhood cancer: a probabilistic model for the incidence of retinoblastoma. Proc Natl Acad Sci USA 72(12):5116–5120

Korsmeyer SJ (1992) Chromosomal translocations in lymphoid malignancies reveal novel proto-oncogenes. Annu Rev Immunol 10:785–807

Kvittingen EA (1991) Tyrosinaemia type I–an update. J Inherit Metab Dis 14(4):554–562

Kwiatkowski DJ (2003) Rhebbing up mTOR: new insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. Cancer Biol Ther 2(5):471–476

Landy SJ, Donnai D (1993) Incontinentia pigmenti (Bloch-Sulzberger syndrome). J Med Genet 30(1):53–59

Levine AJ (1997) p53, the cellular gatekeeper for growth and division. Cell 88(3):323–331

Lewis RJ, Ketcham AS (1973) Maffucci's syndrome: functional and neoplastic significance. Case report and review of the literature. J Bone Joint Surg Am 55(7):1465–1479

Li FP, Fraumeni JF Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, Miller RW (1988) A cancer family syndrome in twenty-four kindreds. Cancer Res 48(18):5358–5362

Limmer J, Fleig WE, Leupold D, Bittner R, Ditschuneit H, Beger HG (1988) Hepatocellular carcinoma in type I glycogen storage disease. Hepatology 8(3):531–537

Lindhurst MJ, et al. (2011) A mosaic activating mutation in AKT1 associated with the proteus syndrome. N Engl J Med 365(7):611–619

Little M, Wells C (1997) A clinical overview of WT1 gene mutations. Hum Mutat 9(3):209–225

Lonser RR, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM, Oldfield EH (2003) von Hippel-Lindau disease. Lancet 361(9374):2059–2067

Lukas J, Parry D, Aagaard L, Mann DJ, Bartkova J, Strauss M, Peters G, Bartek J (1995) Retinoblastoma-protein-dependent cell-cycle inhibition by the tumour suppressor p16. Nature 375(6531):503–506

Lynch HT, de La CA (1999) Genetic susceptibility to non-polyposis colorectal cancer. J Med Genet 36(11):801–818

Maher ER, Eng C (2002) The pressure rises: update on the genetics of phaeochromocytoma. Hum Mol Genet 11(20):2347–2354

Makitie O, Sulisalo T, de la Chapelle A, Kaitila I (1995) Cartilage-hair hypoplasia. J Med Genet 32(1):39–43

Mathew CG (2006) Fanconi anaemia genes and susceptibility to cancer. Oncogene 25(43):5875–5884

Merks JH, Caron HN, Hennekam RC (2005) High incidence of malformation syndromes in a series of 1,073 children with cancer. Am J Med Genet A 134(2):132–143

Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, Hennekam RC (2008) Prevalence and patterns of morphological abnormalities in patients with childhood cancer. JAMA 299(1):61–69

Meyers GA, Orlow SJ, Munro IR, Przylepa KA, Jabs EW (1995) Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. Nat Genet 11(4):462–464

Mohaghegh P, Hickson ID (2001) DNA helicase deficiencies associated with cancer predisposition and premature ageing disorders. Hum Mol Genet 10(7):741–746

Montanaro L, Brigotti M, Clohessy J, Barbieri S, Ceccarelli C, Santini D, Taffurelli M, Calienni M, Teruya-Feldstein J, Trere D, Pandolfi PP, Derenzini M (2006) Dyskerin expression influences the level of ribosomal RNA pseudo-uridylation and telomerase RNA component in human breast cancer. J Pathol 210(1):10–18

Montminy M (1997) Transcriptional regulation by cyclic AMP. Annu Rev Biochem 66:807–822

Moorthy AV, Chesney RW, Lubinsky M (1987) Chronic renal failure and XY gonadal dysgenesis: "Frasier" syndrome–a commentary on reported cases. Am J Med Genet Suppl 3:297–302

Morrison PJ, Nevin NC (1996) Multiple endocrine neoplasia type 2B (mucosal neuroma syndrome, Wagenmann-Froboese syndrome). J Med Genet 33(9):779–782

Mueller RF (1994) The Denys-Drash syndrome. J Med Genet 31(6):471–477

Nadeau JH (2001) Modifier genes in mice and humans. Nat Rev Genet 2(3):165–174

Neri G, Gurrieri F, Zanni G, Lin A (1998) Clinical and molecular aspects of the Simpson-Golabi-Behmel syndrome. Am J Med Genet 79(4):279–283

Nicolaides NC, Papadopoulos N, Liu B, Wei YF, Carter KC, Ruben SM, Rosen CA, Haseltine WA, Fleischmann RD, Fraser CM (1994) Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. Nature 371(6492):75–80

Niihori T, Aoki Y, Narumi Y, Neri G, Cave H, Verloes A, Okamoto N, Hennekam RC, Gillessen-Kaesbach G, Wieczorek D,

Kavamura MI, Kurosawa K, Ohashi H, Wilson L, Heron D, Bonneau D, Corona G, Kaname T, Naritomi K, Baumann C, Matsumoto N, Kato K, Kure S, Matsubara Y (2006) Germline KRAS and BRAF mutations in cardio-facio-cutaneous syndrome. Nat Genet 38(3):294–296

Patton MA (1988) Russell-Silver syndrome. J Med Genet 25(8):557–560

Patton MA, Sharma A, Winter RM (1985) The Aase-Smith syndrome. Clin Genet 28(6):521–525

Paull TT, Gellert M (1999) Nbs1 potentiates ATP-driven DNA unwinding and endonuclease cleavage by the Mre11/Rad50 complex. Genes Dev 13(10):1276–1288

Peto J (2001) Cancer epidemiology in the last century and the next decade. Nature 411(6835):390–395

Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van Ommen GJ, Goodman RH, Peters DJ (1995) Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 376(6538):348–351

Pilarski R, Eng C (2004) Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN hamartoma tumour syndrome. J Med Genet 41(5):323–326

Ponder BA (2001) Cancer genetics. Nature 411(6835):336–341

Pueschel SM (1990) Clinical aspects of Down syndrome from infancy to adulthood. Am J Med Genet Suppl 7:52–56

Rahman N, Scott RH (2007) Cancer genes associated with phenotypes in monoallelic and biallelic mutation carriers: new lessons from old players. Hum Mol Genet 16 Spec No 1:R60–R66

Rauscher FJ III (1993) The WT1 Wilms tumor gene product: a developmentally regulated transcription factor in the kidney that functions as a tumor suppressor. FASEB J 7(10):896–903

Riccardi VM (1977) Trisomy 8: an international study of 70 patients. Birth Defects Orig Artic Ser 13(3C):171–184

Riccardi VM, Sujansky E, Smith AC, Francke U (1978) Chromosomal imbalance in the Aniridia-Wilms' tumor association: 11p interstitial deletion. Pediatrics 61(4):604–610

Ridanpaa M, van Eenennaam H, Pelin K, Chadwick R, Johnson C, Yuan B, van Venrooij W, Pruijn G, Salmela R, Rockas S, Makitie O, Kaitila I, de la CA (2001) Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. Cell 104(2):195–203

Rubinstein JH (1990) Broad thumb-hallux (Rubinstein-Taybi) syndrome 1957–1988. Am J Med Genet Suppl 6:3–16

Ruhrberg C, Williamson JA, Sheer D, Watt FM (1996) Chromosomal localisation of the human envoplakin gene (EVPL) to the region of the tylosis oesophageal cancer gene (TOCG) on 17q25. Genomics 37(3):381–385

Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, Scherer SW, Zhuang Z, Lubensky I, Dean M, Allikmets R, Chidambaram A, Bergerheim UR, Feltis JT, Casadevall C, Zamarron A, Bernues M, Richard S, Lips CJ, Walther MM, Tsui LC, Geil L, Orcutt ML, Stackhouse T, Zbar B (1997) Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet 16(1):68–73

Schuman SH, Burton WE (1979) A new osteosarcoma/malformation syndrome. Clin Genet 15(5):462–463

Scully R (2000) Role of BRCA gene dysfunction in breast and ovarian cancer predisposition. Breast Cancer Res 2(5):324–330

Sijmons RH (ed) Familial Cancer Database. http://www.facd.info.

Sirinavin C, Trowbridge AA (1975) Dyskeratosis congenita: clinical features and genetic aspects. Report of a family and review of the literature. J Med Genet 12(4):339–354

Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, Israel A, Heiss NS, Klauck SM, Kioschis P, Wiemann S, Poustka A, Esposito T, Bardaro T, Gianfrancesco F, Ciccodicola A, D'Urso M, Woffendin H, Jakins T, Donnai D, Stewart H, Kenwrick SJ, Aradhya S, Yamagata T, Levy M, Lewis RA, Nelson DL (2000) Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. Nature 405(6785):466–472

Takahashi M (2001) The GDNF/RET signaling pathway and human diseases. Cytokine Growth Factor Rev 12(4):361–373

Teitz T, Wei T, Valentine MB, Vanin EF, Grenet J, Valentine VA, Behm FG, Look AT, Lahti JM, Kidd VJ (2000) Caspase 8 is deleted or silenced preferentially in childhood neuroblastomas with amplification of MYCN. Nat Med 6(5):529–535

Thakker RV (1998) Multiple endocrine neoplasia–syndromes of the twentieth century. J Clin Endocrinol Metab 83(8):2617–2620

Tlsty TD, Hein PW (2001) Know thy neighbor: stromal cells can contribute oncogenic signals. Curr Opin Genet Dev 11(1):54–59

Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, Leigh I, Gorman P, Lamlum H, Rahman S, Roylance RR, Olpin S, Bevan S, Barker K, Hearle N, Houlston RS, Kiuru M, Lehtonen R, Karhu A, Vilkki S, Laiho P, Eklund C, Vierimaa O, Aittomaki K, Hietala M, Sistonen P, Paetau A, Salovaara R, Herva R, Launonen V, Aaltonen LA (2002) Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet 30(4):406–410

Tsukahara M, Opitz JM (1996) Dubowitz syndrome: review of 141 cases including 36 previously unreported patients. Am J Med Genet 63(1):277–289

Tyldesley WR, Hughes RO (1973) Letter: Tylosis, leukoplakia, and oesophageal carcinoma. Br Med J 4(5889):427

van der Burgt I, Chrzanowska KH, Smeets D, Weemaes C (1996) Nijmegen breakage syndrome. J Med Genet 33(2):153–156

Varon R, Vissinga C, Platzer M, Cerosaletti KM, Chrzanowska KH, Saar K, Beckmann G, Seemanova E, Cooper PR, Nowak NJ, Stumm M, Weemaes CM, Gatti RA, Wilson RK, Digweed M, Rosenthal A, Sperling K, Concannon P, Reis A (1998) Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell 93(3):467–476

Vasen HF, Watson P, Mecklin JP, Lynch HT (1999) New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 116(6):1453–1456

Veale AM, McColl I, Bussey HJ, Morson BC (1966) Juvenile polyposis coli. J Med Genet 3(1):5–16

Villavicencio EH, Walterhouse DO, Iannaccone PM (2000) The sonic hedgehog-patched-gli pathway in human development and disease. Am J Hum Genet 67(5):1047–1054

Viskochil D (1999) Neurofibromatosis 1. Am J Med Genet 89(1):V–VIII

Waite KA, Eng C (2002) Protean PTEN: form and function. Am J Hum Genet 70(4):829–844

Wang LL, Levy ML, Lewis RA, Chintagumpala MM, Lev D, Rogers M, Plon SE (2001a) Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. Am J Med Genet 102(1):11–17

Wang X, Yeh S, Wu G, Hsu CL, Wang L, Chiang T, Yang Y, Guo Y, Chang C (2001b) Identification and characterization of a novel androgen receptor coregulator ARA267-alpha in prostate cancer cells. J Biol Chem 276(44):40417–40423

Wawersik S, Maas RL (2000) Vertebrate eye development as modeled in Drosophila. Hum Mol Genet 9(6):917–925

Weinberg RA (1995) The retinoblastoma protein and cell cycle control. Cell 81(3):323–330

Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM (1991) Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 325(24):1688–1695

Westerman AM, Entius MM, de Baar E, Boor PP, Koole R, van Velthuysen ML, Offerhaus GJ, Lindhout D, de Rooij FW, Wilson JH (1999) Peutz-Jeghers syndrome: 78-year follow-up of the original family. Lancet 353(9160):1211–1215

Winter RM, Baraitser M (2009) The Winter-Baraitser Dysmorphology Database (WBDD). London Medical Databases ltd, London

Wyllie JP, Wright MJ, Burn J, Hunter S (1994) Natural history of trisomy 13. Arch Dis Child 71(4):343–345

Yoo LI, Chung DC, Yuan J (2002) LKB1–a master tumour suppressor of the small intestine and beyond. Nat Rev Cancer 2(7):529–535

Zbar B, Glenn G, Lubensky I, Choyke P, Walther MM, Magnusson G, Bergerheim US, Pettersson S, Amin M, Hurley K (1995) Hereditary papillary renal cell carcinoma: clinical studies in 10 families. J Urol 153(3 Pt 2): 907–912

Zhang Y, Musci T, Derynck R (1997) The tumor suppressor Smad4/DPC 4 as a central mediator of Smad function. Curr Biol 7(4):270–276

Zhou XP, Hampel H, Thiele H, Gorlin RJ, Hennekam RC, Parisi M, Winter RM, Eng C (2001) Association of germline mutation in the PTEN tumour suppressor gene and Proteus and Proteus-like syndromes. Lancet 358(9277): 210–211

Part III

National and International Study Groups

France

7

Daniel Orbach and Yves Reguerre

The incidence of rare, malignant or borderline tumours in children in France is difficult to evaluate at the present time. Only patients with severe, recurrent or complicated forms are referred to oncology departments. The incidence of a large number of rare diseases is therefore severely underestimated, giving a false impression of the true incidence of the disease. The *Registre National des Tumeurs Solides de l'Enfant* (RNTSE) (French Registry of Solid Tumours in Children) provides epidemiological data on childhood cancers in France. However, certain rare tumours are not included in this registry, either because their malignant nature remains uncertain or because they are managed by adult oncology teams or paediatric specialities other than oncology, less accustomed to systematic patient registration. The RNTSE also only records tumours occurring in children under the age of 15 years in metropolitan France. Concomitant registration of borderline tumours is performed but is not comprehensive. The exceptional nature of these diseases as well as their heterogeneous management in terms of both the medical specialty involved (surgery, dermatology, ophthalmology, etc.) and the site of treatment (private clinic or public hospital, paediatric or adult medicine department) account for these difficulties.

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The creation of a rare childhood tumour group by the *Société Française des Cancer de l'Enfant et de l'Adolescent* (SFCE) in November 2006 was the first step designed to address these issues. This group, mainly composed of paediatricians, surgeons, radiotherapists, and pathologists, meets at least twice a year to discuss a specific theme (aggressive vascular tumours, neuroendocrine tumours, mucoepidermoid carcinoma, etc.). Since the creation of this group, diagnostic and treatment guidelines have been proposed for certain tumours such as adrenal cortical adenomas, pleuropulmonary pneumoblastomas, pancreatoblastomas, melanomas, etc., based on retrospective analyses of patients previously treated in France, data of the literature and proposals from the other European or international rare tumour groups. These clinical practice guidelines are then made available to clinicians via the SFCE web site. A local representative responsible for rare tumours has been designated in each of the 30 SFCE centres throughout France to ensure diffusion of these guidelines. The presence of surgeons in the group also ensures close collaboration with the other members of the *Société Française de Chirurgie Pédiatrique* (SFCP). Another objective of this group is to improve the knowledge and treatment of these rare tumours by creating, in collaboration with the SFCE and the RNTSE, a national database for collection of medical information concerning these various diseases. Clinical, laboratory and radiological characteristics, the treatments administered and outcome of the disease will be recorded. Current treatment guidelines, initiated in the context of the SFCE rare tumours group since 2006, constitute the basis for setting up this database. This database therefore concerns diseases corresponding to various histologies, sharing in common their very low incidence (less than

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2 cases per million children under the age of 18) and the absence of formal treatment guidelines. For practical purposes, tumours with an exceptionally low incidence, but for which treatment guidelines or data collection are already available in the context of the SFCE or SIOP working party, will not be included in this group. It was also arbitrarily decided not to include in this rare childhood tumour group those rare haematological malignancies included in the 'leukaemia group'. Consequently, the main diseases concerned by this group are: undifferentiated nasopharyngeal carcinoma; pancreatoblastoma; Frantz's tumour (pseudopapillary tumour of the pancreas); pleuropulmonary blastoma; pseudo-inflammatory tumour; mesothelioma; thymoma; gastrointestinal stromal tumours; desmoplastic small-cell tumour; adrenal cortical adenoma; malignant phaeochromocytoma; carcinoid of the appendix; carcinoid of the small intestine; carcinoid tumour of the bronchus; midline carcinoma; aggressive giant-cell bone tumours; chondroblastoma; chondrosarcoma; malignant head and neck tumours: sialoblastoma, mucoepidermoid carcinoma, aggressive benign vascular tumour, lung carcinomas, urothelial carcinomas and chordomas. Some tumours that are common in adults but rare in children will also be included in this database when they occur in children, such as cutaneous or choroidal malignant melanomas, ocular medulloepitheliomas, breast cancers, colon cancers or thyroid cancers.

Germany

8

Ines B. Brecht and Dominik T. Schneider

Content

The German Childhood Cancer Registry (GCCR) annually registers approx. 1,800 children diagnosed with a malignant disease (completeness of registration >95%) (Kaatsch 2004). While most pediatric cancer patients are diagnosed and treated according to standardized cooperative protocols of the German Society for Pediatric Oncology and Hematology (GPOH), a significant proportion of patients with rare tumors do not fully benefit from the sophisticated network, including study and reference centers (Schneider and Brecht 2010). Only recently, major attention has been drawn to the diagnostic assessment and treatment of children and adolescents with such orphan diseases. However, compared to other national pediatric oncologic cooperative groups, the infrastructure for rare tumors in children and adolescents is particular in Germany. Thus, a variety of rare cancers have already been integrated into cooperative protocols and prospective therapy optimization trials. Among others, these include endocrine cancers (e.g., thyroid cancers, adrenocortical carcinoma, and carcinoids), nasopharyngeal carcinoma, rare gonadal tumors, and rare soft tissue sarcomas. Nevertheless, with the advent of the new EU regulation on clinical trials, no new prospective trials have recently been developed for rare childhood cancers. Instead, the abovementioned protocols have been developed into clinical registries that include a therapeutic guidance based on the current standard treatment, central clinical data collection, and support of coordinated molecular genetic studies.

Nevertheless, there remains a group of patients with rare tumors that are diagnosed and treated outside of the diagnostic, therapeutic, and scientific network of the GPOH. Based on a retrospective analysis of data from the GCCR, it is assumed that in Germany,

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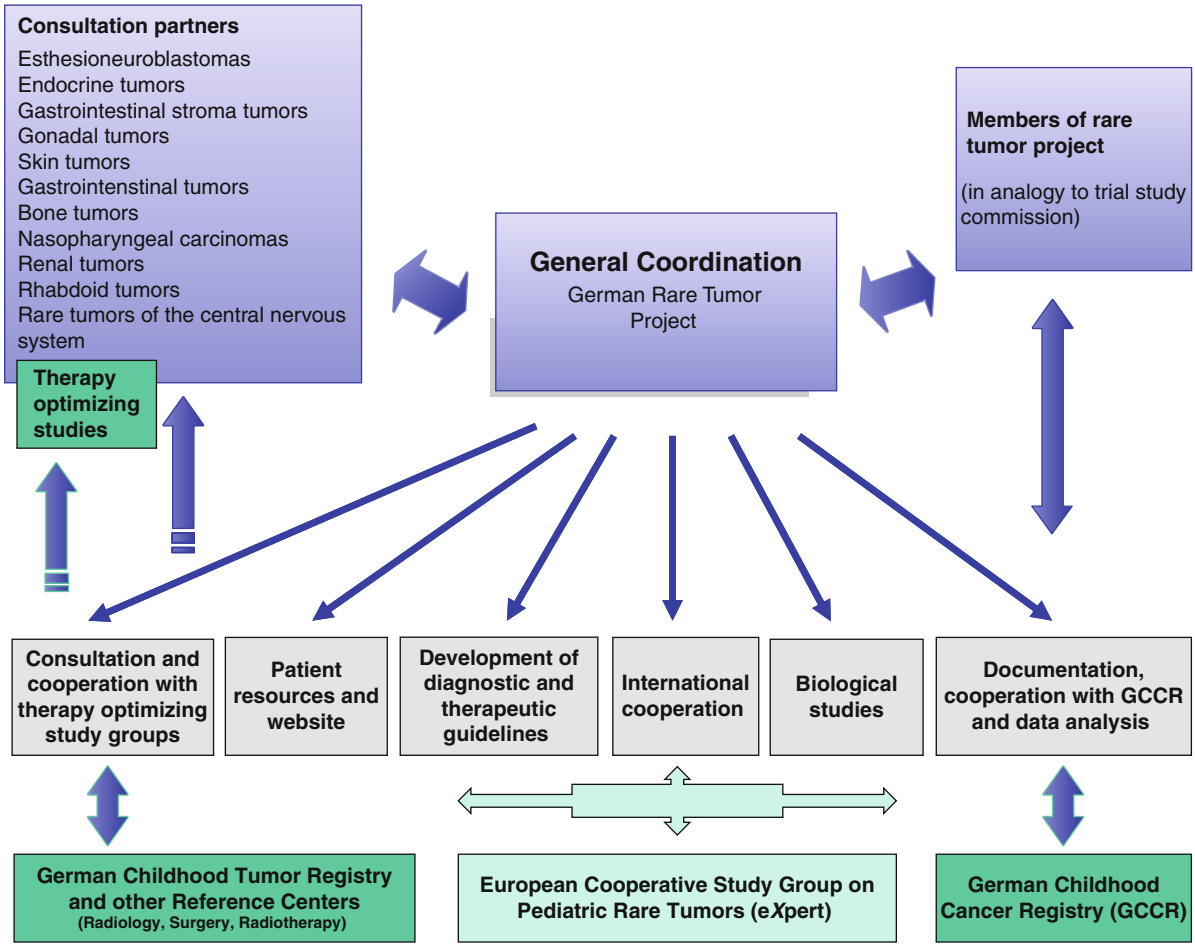

Fig. 8.1 Network structure of the German Rare Tumor Group

annually about 50 children and adolescents (5% of all malignancies) with such rare cancers will be diagnosed (Brecht et al. 2009). In order to support the clinical management of these patients, to facilitate clinical consultation, and to foster research on such rare tumors, the GPOH Rare Tumor Group was founded in 2006. It constitutes a working group that includes experts from Pediatric Oncology, Pediatric Surgery, Pediatric Pathology, Medical, ENT specialists, Dermatologic and Radiation Oncology, as well as Pediatric Epidemiology. The structure of the German working group (STEP – Seltene Tumorerkrankungen in der Pädiatrie (Rare Tumors in Pediatrics)) is shown in Fig. 8.1. STEP is coordinated cooperatively at the study centers in Dortmund and Erlangen. The members of the working group focused their scientific work on rare pediatric tumor entities and/or coordinated clinical registries or trials for other rare tumor entities (Table 8.1). Through the close cooperation with the existing study groups as well as reference centers of the GPOH, including pediatric pathology, GCCR, the competence center, and the Biocase project – a central tumor banking project – of the GPOH, patients with rare pediatric tumors shall be lead into the diagnostic and therapeutic reference network.

Thus, the main goals, similar to those of other national and international tumor groups, are:

- To promote the exchange of clinical experience in patients with rare tumors between centers,
- To strengthen the registration of patients with rare tumors by active data accrual,
- To generate information by the collection and evaluation of clinical data in a clinical registry and to develop diagnostic and therapeutic recommendations,

Table 8.1 Clinical trials and registries for rare pediatric tumors within the Society for Pediatric Oncology and Hematology (GPOH)

Rare tumor entity	Clinical trial center/registry
Liver tumors	*Liver Tumor Registry* Prof. Dietrich von Schweinitz, M.D., Munich dietrich.schweinitz@med.uni-muenchen.de
Endocrine tumors	*Study Registry for Malignant Endocrine Tumors in Children and Adolescents (MET)* Peter Vorwerk, M.D., Magdeburg peter.vorwerk@med.ovgu.de
Rare soft tissue sarcomas	*SoTiSar Registry* Prof. Ewa Koscielniak, M.D. and Prof. Thomas Klingebiel, M.D., Stuttgart, Frankfurt cws@olgahospital-stuttgart.de
Esthesioneuroblastoma	*Registry associated with the German Neuroblastoma Study* Barbara Hero, M.D., Cologne barbara.hero@uk-koeln.de
Gastrointestinal stromal tumors	*Registry associated with the SoTiSar Registry* Martin Benesch, M.D., Graz, Austria martin.benesch@klinikum-graz.at
Rare gonadal tumors	*MAKEI Study for Maligne Keimzelltumoren* Prof. Dominik T. Schneider, M.D., Dortmund dominik.schneider@klinikumdo.de
Nasopharyngeal carcinoma	*Nasopharynxkarzinom NPC-2003-GPOH* Prof. Rolf Mertens, M.D., Aachen rmertens@ukaachen.de
Rare kidney tumors/ renal cell carcinoma	*Registry associated to the SIOP/ GPOH Nephroblastoma Study* Barbara Selle, M.D./Prof. Norbert Graf, M.D., Berlin, Homburg/Saar norbert.graf@uniklinikum-saarland.de
Rhabdoid tumors	*European Registry for Rhabdoid Tumors (EU-RHAB)* Prof. Michael Frühwald, Ph.D., M.D., Augsburg michael.fruehwald@klinikum-augsburg.de

- To facilitate the physicians' and patients' access to information on rare pediatric tumors by introducing a specific website within www.kinderkrebsinfo.de.
- To support clinical and biological research projects on rare tumors.

For this purpose, a consultation and reference center for rare pediatric tumors is coordinated in Dortmund, aiming to quickly provide direct medical advice to inquiries of patients and attending physicians (contact: dominik.schneider@klinikumdo.de).

In October 2008, the active data accrual has started by the distribution of a short registration sheet to all pediatric oncologic and pediatric surgical hospitals in Germany, Austria, and Switzerland. Until March 2011, STEP registered 120 patients from 38 hospitals, treated with a rare pediatric tumor since 2006 and not registered in one of the other clinical trials of the GPOH. The largest groups were malignant melanoma; head and neck tumors, in particular salivary gland tumors; and tumors of the gastrointestinal tract.

Further, more detailed prospective disease-specific analyses are coordinated in Erlangen. For this purpose, documentation sheets for the different entities are developed in international cooperation with the members of the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT) (see separate chapter 13) in order to allow common analyses and development of diagnostic and therapeutic guidelines. Also, data are continuously exchanged with the German Childhood Cancer Registry (GCCR) (contact: ines.brecht@uk-erlangen.de).

This scientific and clinical network shall ultimately help to integrate children and adolescents with rare cancers into the infrastructure of the national and international childhood cancer societies.

References

Brecht IB, Graf N et al (2009) Networking for children and adolescents with very rare tumors: foundation of the GPOH Pediatric Rare Tumor Group. Klin Pädiatr 221(3): 181–185

Kaatsch P (2004) German Childhood Cancer Registry and its favorable setting. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 47(5):437–443

Schneider DT, Brecht IB (2010) Care for rare cancers: improved care requires improved communication. Klin Pädiatr 222(3): 124–126

Italy

9

Andrea Ferrari

Content

A national-scale cooperative project focusing on rare (or very rare) pediatric tumors and called the TREP project (Tumori Rari in Età Pediatrica [*Rare Tumors in Pediatric Age*]) was launched in Italy in 2000 under the auspices of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), and in cooperation with the Società Italiana Chirurgia Pediatrica (SICP) (Ferrari et al. 2007).

To clearly define its area of interest, the TREP group adopted a pragmatic definition of "*rare pediatric tumors*," considering practical and clinical issues rather than epidemiological data and including any solid malignancy characterized by an annual incidence <2 per million and not considered in other clinical trials. As a consequence of this definition, the TREP project did not include tumors with such a low incidence but already "covered" by other national studies, i.e., renal rhabdoid tumors were registered in the with AIEOP Wilms Tumor Study, hepatoblastoma and malignant germ cell tumors had their own protocols, rare histotypes of soft part sarcomas were covered by the cooperative study on soft tissue sarcomas, and so on. The definition adopted was considered suitable for classifying the "orphan" tumors in the Italian pediatric setting. An assortment of tumors was thus involved, including some neoplasms that are rare at any age, but also (and mainly) tumors that are rare in childhood and adolescence but more common in adulthood, e.g., nasopharyngeal carcinoma, adrenocortical tumors, pleuropulmonary blastoma (and other lung tumors), carcinoid tumors, cutaneous melanoma, renal cell carcinoma, pancreatoblastoma (and other pancreatic exocrine tumors), gonadal non-germ-cell tumors (ovary/testis), pheochromocytoma and paraganglioma, thyroid carcinoma, salivary gland tumors, breast carcinoma, carcinoma of the gastrointestinal tract, and carcinoma of the thymus.

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The main aims of the TREP project were:

1. To develop diagnostic and therapeutic recommendations for each rare tumor, based on single-institutional or cooperative retrospective reviews conducted on specific tumor types (Indolfi et al. 2000, 2003, 2007; Casanova et al. 2001, 2003; Spinelli et al. 2004; Dall'Igna et al. 2005; Ferrari et al. 2005, 2008; Collini et al 2006; Massimino et al. 2006; Guzzo et al. 2006);
2. To collect clinical data by using specific printed forms for diagnostic work-up, treatment, and follow-up (a centralized Data Center was set up, at the Clinical Trials and Biostatistics Unit of the Istituto Oncologico Veneto in Padova, Italy, supported by private grants from the "Fondazione Città della Speranza," Padova, and the "Fondazione CARIPARO");
3. To identify one (or more) researcher(s) "dedicated" to each histotype who could act as an expert to consult Table 9.1
4. To create a network for cooperation with other specialists (adult oncologists and surgeons, endocrinologists, dermatologists, gastroenterologists, etc.) involved in managing these tumors; and
5. To organize pathological and biological studies.

From January 2000 to December 2009, 540 patients <18 years of age were registered in the TREP database, which means a rate of more than 50 patients a year, as compared with 15 cases a year collected in a historical retrospective AIEOP study (Cecchetto et al. 1995). Patients were registered by 38 different Italian centers, confirming the broad adhesion to the project. Patients range in age from 12 days to 18 years, median 12 years (69% of cases were over 10 years old); 59% of all cases are female. Thyroid carcinoma proved the most common histotype, followed by carcinoid tumors, skin tumors, gonadal non-germ-cell tumors, and nasopharyngeal carcinoma Fig. 9.1.

An analysis performed in cooperation with the AIEOP Epidemiology group compared the number of cases actually registered (between 2000 and 2006) with the number of cases predicted in the light of incidence data in the Italian population-based cancer registries (AIRTum). The number of rare pediatric tumors predicted to occur in Italy between 2000 and 2006 was 305 among the 0–14-year-olds and 400 among the 15–17-year-olds (on average, 44 children and 57 adolescents are expected to develop a rare pediatric tumor each year), while the numbers of cases actually identified by the TREP were 261 and 75, respectively. For the 0–14-year-olds, the ratio of observed to expected cases was even 1:1 for several tumors (i.e., nasopharyngeal carcinoma, adrenocortical tumors, renal cell carcinoma, and gonadal non-germ-cell tumors), while for the adolescents underreporting was statistically significant for all tumor types except nasopharyngeal carcinoma (Pastore et al. 2009). These findings were generally regarded as an indication of the TREP project's success (the vast majority of patients with rare pediatric tumors under 15 years of age were registered and treated according to TREP guidelines, http://trep-project.org), and of the feasibility of cooperative protocols even for rare diseases. The underreporting of adolescents was similar to what was seen also for the more-common pediatric malignancies.

What are the key elements of the TREP project and the lessons learned from it?

First, the dual need of the project, i.e., to prompt research and to provide all centers with practical patient management schemes. In Italy, there was a shortage of information on these rare pediatric tumors, and doctors were calling for treatment guidelines; the various experts involved in the project have been able to offer a real advisory service.

Second – and consequently – the importance of developing a network involving several centers and specialists from different branches of medicine and science.

Third, the adoption of a common framework: the different working groups (one for each tumor type) developed their "protocols" in the context of the same structured manner, and this ensured homogeneous methods and guaranteed the discipline essential to the efficacy of cooperative clinical trials (Ferrari 2009).

In conclusion, the TREP project demonstrates that cooperative prospective research and treatment guidelines on very rare pediatric cancers can be done, within a common framework, on a national scale at least. The people involved in the TREP project have had the distinct feeling that their knowledge of these tumors has increased and, more importantly, that this has improved the quality of patient care they can provide.

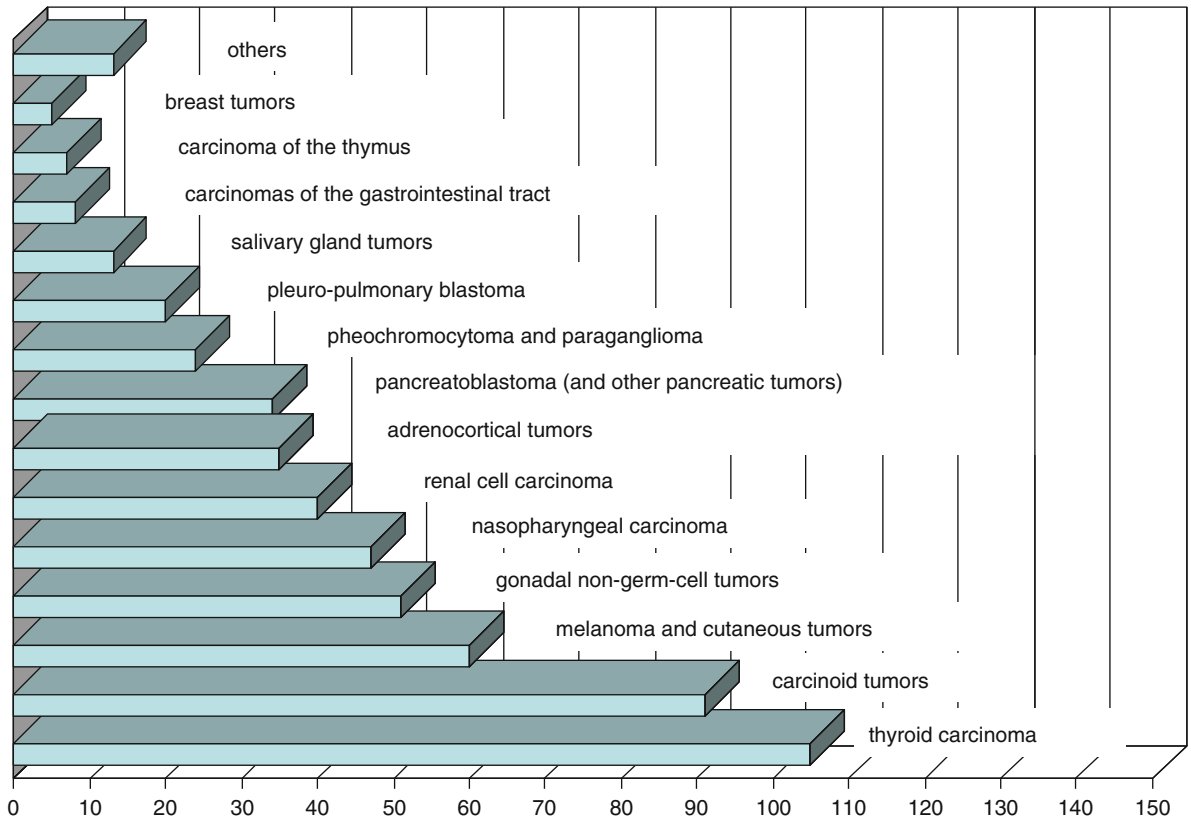

Fig. 9.1 Tumor types registered in the trep project from january 2000 to december 2009

Table 9.1 TREP working group

Website: http://trepproject.org: structure of the group, centers and members involved, projects and activity, news, meetings, publications; members' area with diagnostic and treatment guidelines for each tumor types
Founders and coordinators: Gianni Bisogno (Padova University), Giovanni Cecchetto (Padova University), Andrea Ferrari (Istituto Nazionale Tumori Milano)
Data Center: Clinical Trials and Biostatistics Unit of the Istituto Oncologico Veneto in Padova, Italy, coordinated by Gian Luca De Salvo and supported by private grants from the "Fondazione Città della Speranza," Padova, and the "Fondazione CARIPARO"
Disease-specific responsible researchers:
Nasopharyngeal carcinoma – Michela Casanova, Andrea Ferrari, Lorenza Gandola
Adrenocortical tumors – Giovanni Cecchetto, Gianni Bisogno
Pleuropulmonary blastoma – Gianni Bisogno, Paolo Indolfi
Carcinoid tumors – Patrizia Dall'Igna, Giovanni Cecchetto
Cutaneous melanoma – Andrea Ferrari, Aldo Bono
Renal cell carcinoma – Paolo Indolfi, Giovanni Cecchetto, Filippo Spreafico
Pancreatoblastoma – Patrizia Dall'Igna, Andrea Ferrari
Gonadal non-germ-cell tumors (ovary/testis) – Giovanni Cecchetto, Gabriella Bernini
Pheochromocytoma and paraganglioma – Gianni Bisogno, Giovanni Cecchetto
Thyroid carcinoma – Maura Massimino, Claudio Spinelli, Alessandro Inserra
Salivary gland tumors – Andrea Ferrari, Marco Guzzo
Carcinoma of the gastrointestinal tract – Andrea Ferrari, Alessandro Inserra
Carcinoma of the thymus – Gianni Bisogno, Alessandro Inserra
Gastrointestinal stromal tumor – Andrea Ferrari, Gianni Bisogno
Pathology Committee: Gaetano Magro, Rita Alaggio, Paola Collini, Nunzio Salfi, Claudio Gambini, Renata Boldrini

References

Casanova M, Ferrari A, Gandola G et al (2001) Undifferentiated nasopharyngeal carcinoma in children and adolescents: comparison between staging systems. Ann Oncol 12:1157–1162

Casanova M, Collini P, Ferrari A et al (2003) Solid-pseudopapillary tumor of the pancreas (Frantz tumor) in children. Med Pediatr Oncol 41:74–76

Cecchetto G, Allegretto C, Giuliano M et al (1995) Rare pediatric malignant tumors: a retrospective Italian cooperative study. SIOP XXVII Meeting, Montevideo (Uruguay), Med Pediatr Oncol 25:348

Collini P, Massimino M, Fagundes Leite S et al (2006) Papillary thyroid carcinoma of childhood and adolescence. A 30-year monoinstitutional series of the Istituto Nazionale Tumori of Milan. Pediatr Blood Cancer 46:300–306

Dall'Igna P, Ferrari A, Luzzatto C et al (2005) Carcinoid tumor of the appendix in childhood: the experience of two Italian Institutions. J Pediatr Gastroenterol Nutr 30:216–219

Ferrari A (2009) The challenge of very rare pediatric tumors: the Italian TREP project. Educational Book, American Society of Clinical Oncology Annual Meeting: 620–624

Ferrari A, Bono A, Baldi M et al (2005) Does melanoma behave better in younger children than in adults? A retrospective study on 33 cases of childhood melanoma from a single institution. Pediatrics 115:649–654

Ferrari A, Bisogno G, De Salvo GL et al (2007) The challenge of very rare tumours in childhood: the Italian TREP project. Eur J Cancer 43:654–659

Ferrari A, Rognone A, Casanova M et al (2008) Colorectal carcinoma in children and adolescents: the experience of the Istituto Nazionale Tumori of Milan, Italy. Pediatr Blood Cancer 50(3):588–593

Guzzo M, Ferrari A, Marcon I et al (2006) Salivary gland neoplasms in pediatric age: the experience of the Istituto Nazionale Tumori of Milan. Pediatr Blood Cancer 47: 806–810

Indolfi P, Casale F, Carli M et al (2000) Pleuropulmonary blastoma: management and prognosis of 11 cases. Cancer 89:1396–1401

Indolfi P, Terenziani M, Casale F et al (2003) Renal cell carcinoma in children: a clinico-pathological study in 41 cases. J Clin Oncol 21:530–535

Indolfi P, Bisogno G, Casale F et al (2007) Prognostic factors in pleuro-pulmonary blastoma. Pediatr Blood Cancer 48: 318–323

Massimino M, Collini P, Fagundes Leite S et al (2006) Conservative surgical approach for thyroid and lymph-node involvement in papillary thyroid carcinoma of childhood and adolescence. Pediatr Blood Cancer 46:307–313

Pastore G, De Salvo GL, Bisogno G et al (2009) Evaluating the access to pediatric cancer care centres of children and adolescents with rare tumors in Italy: the TREP project. Pediatr Blood Cancer 53:152–155

Spinelli C, Bertocchini A, Antonelli A, Miccoli P (2004) Surgical therapy of the thyroid papillary carcinoma in children: experience with 56 patients < or =16 years old. J Pediatr Surg 39:1500–1505

Poland

10

Jan Godzinski

Content

Polish Paediatric Solid Tumours Study Group (in Polish: Polska Pediatryczna Grupa Guzów Litych (PPGGL)) was created in 1992 in Poznań. During the first 10 years of activity, PPGGL developed, adapted or joined international therapeutic programs for majority of common paediatric malignancies. Studies on soft tissue sarcomas, neuroblastoma and renal tumours are best examples. Further development of the group continued, and in 2002, new study was launched and named Polish Paediatric Rare Tumours Study Group. The core committee were Anna Balcerska (chair)[a], Jan Godzinski (paediatric surgeon, co-chair)[b], Ewa Bien (paediatric oncology consultant)[a], Teresa Stachowicz-Stencel (paediatric oncology consultant)[a] and Malgorzata Rapala (data management and statistics)[b]. The interest of the group focused on those malignancies which had extremely low incidence and were not included in other already existing therapeutic protocols. Study started its activity with the call for retrospective data on rare tumours from preceding decade in order to build a core database. This database served for number of retrospective reviews on particular diseases presented and published widely. The second objective was current registration of new cases and building an expert advice platform basing on the experience gained thus far, collected literature bank and, to some extent, the contacts with experts identified for particular malignancies. The consultation platform and data bank organised by Rare Tumours Study Committee serve not only to the paediatric oncology centres cooperating within PPGGL but also to general paediatricians and other specialists if request. Useful addresses are at the bottom of this page. In 2008, Polish Paediatric Rare Tumours Study entered formalised cooperation with similar national groups from Italy, Germany, United Kingdom and France,

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which all together formed international working group called ExPERT. Two first common ExPERT analyses were wider presented during SIOP annual meeting in Boston in 2010 and considered pancreatoblastomas and Sertoli–Leydig cells tumours. Polish Rare Tumours Study Group participated in both.

Until the end of 2010, the group published 28 full-text papers and congress abstracts on different aspect of paediatric rare tumours in national and international medical journals. Those published in English are listed as references to this section (Bień et al. 2004, 2009a, b; Godziński et al. 2004; Stachowicz-Stencel et al. 2004, 2010).

Polish Paediatric Rare Tumours Study Committee

Useful addresses:

(a) Head Quarter and Data Bank: Department of Paediatrics, Haematology, Oncology and Endocrinology. Medical University of Gdansk, 7 Dębinki Street, 80–211 Gdańsk, Poland

(b) Surgical Head Quarter and Statistics: Department of Paediatric Surgery, Marciniak Hospital, Traugutta 116, 50–420 Wroclaw, Poland

References

Bień E, Stachowicz-Stencel T, Balcerska A, Godziński J, Rąpała M, Sulka W, Drogosiewicz M, Klekawka T, Kurylak A, Madziara W, Nurzyńska-Flak J, Perek-Polnik M, Pietras W, Wolf-Tybura M, Balwierz W, Bohosiewicz J, Chybicka A, Kowalczyk J, Perek D, Stoba C, Wysocki M (2004) Incidence, characteristics and outcome of the alimentary tract carcinomas (Atc) in children: Report from the Polish Paediatric Rare Tumours Study. In: Chybicka A, Kazanowska B, Toporski J (eds) Advances in pediatric bone marrow transplantation and oncology. Medical University of Wrocław, Wrocław, pp 198–202

Bień E, Stachowicz-Stencel T, Balcerska A, Godziński J, Kazanowska B, Perek-Polnik M, Madziara W, Rybczyńska A, Kurylak A, Zalewska-Szewczyk B, Peregud-Pogorzelski J (2009a) Angiosarcoma in children – still uncontrollable oncological problem: the report of the polish paediatric rare tumours study. Eur J Cancer Care 18(4):411–420

Bień E, Stachowicz-Stencel T, Godziński J, Balcerska A, Iżycka-Świeszewska E, Kazanowska B, Madziara W, Perek-Polnik M, Mankowski P, Nurzyńska-Flak J, Rybczyńska A, Prokurat A (2009b) Retrospective multi-institutional study on hemangiopericytoma in polish children. Pediatr Int 51:19–24

Godzinski J, Bień E, Pietras W, Stachowicz-Stencel T, Balcerska A, Rąpała M, Sulka W, Bohosiewicz J, Drogosiewicz M, Jankowski A, Jeleń M, Kowalczyk J, Kurylak A, Madziara W, Mańkowski P, Nurzyńska-Flak J, Perek-Polnik M, Perek D, Wysocki M (2004) Melanoma in children: same or different as in adults. In: Chybicka A, Kazanowska B, Toporski J (eds) Advances in pediatric bone marrow transplantation and oncology. Medical University of Wroclaw, Wroclaw, pp 223–225

Stachowicz-Stencel T, Bień E, Sierota D, Drożyńska E, Jaśkiewicz K, Balcerska A, Godziński J (2004) Renal cell carcinoma (Rcc) 10 years after chemotherapy for stage IV neuroblastoma: the only case of secondary RCC in the Polish Rare Tumours Study. In: Chybicka A, Kazanowska B, Toporski J (eds) Advances in pediatric bone marrow transplantation and oncology. Medical University of Wrocław, Wroclaw, pp 249–253

Stachowicz-Stencel T, Bień E, Balcerska A, Godziński J, Synakiewicz A, Madziara W, Perek-Polnik M, Peregud-Pogorzelski J, Pietras W, Pobudejska A, Kurylak A, Mankowski P (2010) Thymic carcinoma in children: a report from the Polish Pediatric Rare Tumors Study. Pediatr Blood Cancer 54(7):916–920

The United Kingdom

11

Bernadette Brennan

Content

Cancer is rare in childhood compared with older age groups, affecting approximately 1 in 600 children during the first 15 years of life. However, some tumours are so rare that even paediatric oncologists may only encounter them once in their lifetime practice. Any definition of 'rare' is bound to be arbitrary, but a suggested definition of rare childhood cancers are those categories in the International Classification of Childhood Cancer [third edition (ICCC-3)], that have an age-standardised annual incidence of less than 1 per million children in the UK, excluding tumours of unspecified morphology (Steliarova-Foucher et al. 2005). Based on the UK National Registry of Childhood Tumours (NRCT), Table 11.1 describes the incidence rates and numbers of registrations in Britain during 1991–2000 for rare childhood cancers according to this definition, excluding leukaemias, lymphomas and CNS tumours.

Histological subtypes of germ cell tumours which individually have incidence below 1 per million have also been excluded on the grounds that clinically all malignant germ cell tumours in children are treated similarly. Overall, the tumours listed in Table 11.1 had

- An incidence rate of 6.8 per million,
- Accounted for 16% of non-CNS malignant solid tumours
- Accounted 5% of all childhood cancers.
- In both relative and absolute terms they were most frequent in the age group 10–14 years, where their incidence was 12.4 per million and where they accounted for 35% of non-CNS solid tumours and 11% of all cancers.

Carcinomas of all sites counted as rare tumours, and collectively formed 50% of the total. Soft tissue sarcomas were the next most frequent histological

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Table 11.1 Rare childhood cancers in Great Britain, 1991–2000. Age standardized annual incidence per million children aged 0–14 years (ASR) and number of registrations (N). Leukaemias, lymphomas and CNS tumours are excluded

ICCC-3 Definition		ASR	N
IV	*Neuroblastoma and other peripheral nervous cell tumours*		
IVb	Peripheral nervous cell tumours other than neuroblastoma	0.10	11
VI	*Renal tumours*		
VIa.2	Rhabdoid renal tumour	0.36	24
VIa.3	Kidney sarcomas	0.36	24
VIa.4	Peripheral PNET of kidney	0.05	7
VIb	Renal carcinoma	0.16	19
VII	*Hepatic tumours*		
VIIb	Hepatic carcinoma	0.22	25
VIII	*Malignant bone tumours*		
VIIIb	Chondrosarcoma	0.10	12
VIIId	Other specified malignant bone tumours	0.14	16
IX	*Soft tissue and other extraosseous sarcomas*		
IXb.1	Fibroblastic and myoblastic tumours	0.35	37
IXb.2	Nerve sheath tumours	0.36	41
IXb.3	Other fibromatous neoplasms	0.02	2
IXc	Kaposi sarcoma	0.04	5
IXd.3	Extrarenal rhabdoid tumour	0.20	19
IXd.4	Liposarcomas	0.04	4
IXd.5	Fibrohistiocytic tumours	0.41	47
IXd.6	Leiomyosarcomas	0.10	12
IXd.7	Synovial sarcomas	0.49	58
IXd.8	Blood vessel tumours	0.11	11
IXd.9	Osseous and chondromatous neoplasms of soft tissue	0.08	9
IXd.10	Alveolar soft part sarcoma	0.09	10
IXd.11	Miscellaneous soft tissue sarcomas	0.18	19
X	*Germ cell tumours, trophoblastic tumours and neoplasms of gonads*		
Xd	Gonadal carcinomas	0.07	8
Xe	Other malignant non germ cell gonadal tumours	–	0
XI	*Other malignant epithelial neoplasms and malignant melanomas*		
XIa	Adrenocortical carcinoma	0.24	24
XIb	Thyroid carcinoma	0.60	71
XIc	Nasopharyngeal carcinoma	0.20	24
XIe	Skin carcinomas	0.70	82
XIf.1	Carcinomas of salivary glands	0.25	30
XIf.2	Carcinomas of colon and rectum	0.09	11
XIf.3	Carcinomas of appendix	0.12	15
XIf.4	Carcinomas of lung	0.08	10
XIf.5	Carcinomas of thymus	0.03	4
XIf.6	Carcinomas of breast	–	0
XIf.7	Carcinomas of cervix uteri	0.01	1
XIf.8	Carcinomas of bladder	0.05	6
XIf.9	Carcinomas of eye	–	0
XIf.10	Carcinomas of other specified sites	0.33	39
XIf.11	Carcinomas of unspecified site	0.11	12
XII	*Other and unspecified malignant neoplasms*		
XIIa.1	Gastrointestinal stromal tumour	0.02	2
XIIa.2	Pancreatoblastoma	0.04	4

Table 11.1 (continued)

ICCC-3 Definition		ASR	N
XIIa.3	Pulmonary blastoma and pleuropulmonary blastoma	0.08	8
XIIa.4	Other complex mixed and stromal neoplasms	–	0
XIIa.5	Mesothelioma	0.03	3
XIIa.6	Other specified malignant tumours	–	0
	Total of non-CNS rare tumours	*6.79*	*766*
	Total of all non-CNS solid tumours	*46.18*	*4,770*
	Total childhood cancers	*139.19*	*14,659*

Source: National Registry of Childhood Tumours (Stiller 2007)

group, representing 36%. It is important to note that the same diagnostic groups are not necessarily rare in all populations. Most strikingly, Kaposi sarcoma is one of the most frequent childhood cancers in parts of central and east Africa most severely affected by the AIDS epidemic, whereas malignant melanoma is rare throughout most of Africa and Asia.

Despite their rarity, the tumours described can cause much stress to both the families and the oncologist. However, rare tumours do not necessarily have a poor prognosis, and some tumour types may be easily treated and have very little chance of recurring. These include some tumours that are rare among children but occur more commonly in adults and we can learn a lot from their management in this setting so that this can be adapted for their treatment in childhood. A good example for this can be found for thyroid carcinoma (the follicular subtype is most commonly encountered in the paediatric population), where the 5-year survival for the 71 children diagnosed in Britain during 1991–2000 was 100% (Stiller 2007).

Other rare tumours, however, only occur in childhood or are currently have a poor prognosis. This focus therefore was the starting point for the Rare Tumour Guidelines that were produced by the Rare Tumour Working Group of the CCLG. In particular, we also included nasopharyngeal carcinoma, as this is one of the rare tumours frequently consulted about because of its challenging treatment, and as an example of a rare tumour where there has been a dramatic improvement in survival in recent years.

From about 1997 various members of the CCLG Rare Tumour Working Group took charge pulling together guidance for several rare tumours. The format consisted of the known data from the UK National Registry of Childhood Tumours (NRCT) and an up to date review of the literature using this to conclude guidance around management, diagnosis and treatment. Where possible information regarding open International registries/protocols was also made available. The list of the current Rare Tumour Guidelines available to members on the CCLG website or incorporated into study protocols or published are listed in Table 11.2.

Table 11.2 CCLG Rare Tumour Guidelines

Guideline	Author	Comments
Thymic epithelial tumours	Paula Shaw Richard Grundy Bernadette Brennan	CCLG website
Pleuropulmonary blastoma	Anthony Ng Julia Chisholm	Part of international collaboration on PPB
Nasopharyngeal Carinoma	Bernadette Brennan	CCLG website
Extracranial rhabdoid tumour	Bernadette Brennan	Part of EpSSG non rhabdomyosarcoma tumour protocol 2005.
Pancreatic tumours	Murray Yuile Bernadette Brennan	CCLG website
Adrenocortical tumours	Richard Grundy	CCLG website
CNS DNET Meningioma	Connor Mallucci Heidi Traunecker	British Journal Neurosurgery
Melanoma	Ross Pinkerton	CCLG website
Melanotic Neuroectodermal tumours	Helen Jenkinson	CCLG website

In 2005 a multi-disciplinary consensus statement of best practice for the management and treatment for paediatric endocrine tumours from a working group convened under the auspices of the BSPED (British Society of Paediatric Endocrinology and Diabetes) and CCLG (rare tumour working groups) was published as a booklet available to all members. The working group was multidisciplinary consisting

of paediatric endocrinologists, oncologists and surgeons together with adult surgeons, oncologists and clinical geneticists with paediatric expertise. The following endocrine tumours were covered in the booklet:

Craniopharyngioma
Adreno-cortical Neoplasms
Phaeochromocytoma
Thyroid Carcinoma (Differentiated)
Medullary Thyroid Carcinoma and Multiple Endocrine Neoplasia Type 2 (MEN 2) syndromes
Parathyroid and Pituitary Tumours (including primary hyperparathyroidism) and Multiple Endocrine Neoplasia Type 1 (MEN1) syndromes

Although the registration of these rare tumours continues in the UK in the NRCT for patients 15 years and under, it is less complete for older teenagers and contains limited details on treatment received and factors which maybe important for prognosis such as tumour dimensions, sites of metastases etc. The quality of the data may improve in the future with the National Cancer Dataset project run by the National Cancer Intelligence Network where the information collected in the UK cancer registries will increase for all cancers including rare tumours in childhood.

References

Steliarova-Foucher E et al (2005) International classification of childhood cancer, third edition (ICCC-3). Cancer 103(7):1457–1467

Stiller C (2007) Childhood cancer in Britain: incidence, survival, mortality. Oxford University Press, Oxford

The United States

12

Farzana D. Pashankar
and Carlos Rodriguez-Galindo

Contents

12.1 Introduction

In the United States, every year, 12,000 children and adolescents less than 20 years old are diagnosed with cancer. Based on the experience gained in other national and international rare tumor groups, the COG Rare Tumor Committee chose to define infrequent tumors within the context of a pediatric population as those neoplasms, which are generally classified as other malignant epithelial neoplasms and melanomas in the International Classification of Childhood Cancer subgroup XI of the SEER database (Pappo et al. 2010). Thus, included in the rare tumor group were a large number of tumors with a varied biology and clinical presentation as outlined in Table 12.1. Other tumors that are rare but were not included as they have their own clinical trials are malignant germ cell tumors, hepatoblastoma, renal rhabdoid tumors, and rare histiotypes of soft tissue sarcomas.

Although rare as individual tumors, in aggregate, these tumors account for 15% of all cancers in children <20 years and 30% of all tumors in children between the ages 15 and 19 years (Fig. 12.1) (Ries et al. 1999).

12.2 Children's Oncology Group (COG) Rare Tumor Committee

There are considerable challenges associated with studying rare tumors (see Chap. 1). In order to overcome some of these difficulties, the COG Rare Tumor Initiative was developed in 2002. Three subcommittees were established – germ cell, liver, and infrequent tumors. In 2008, the Retinoblastoma and Rare Tumor Committees merged into the current Rare Tumor

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Table 12.1 Tumors included in the COG Rare Tumor Committee

Infrequent tumors monitored by the COG Rare Tumor Committee
• Thyroid carcinomas
• Colorectal carcinomas
• Nasopharyngeal carcinomas
• Adrenocortical carcinomas
• Desmoplastic small round cell tumor
• Melanoma
• Pancreatoblastoma
• Gastrointestinal stromal tumors
• Gonadal stromal tumors
• Neuroendocrine tumors
Rare tumors with clinical trials
• Retinoblastoma
• Malignant germ cell tumors
• Hepatoblastomas
• Renal and extrareanl rhabdoid tumors
• Rare histiotypes of soft tissue sarcomas

Committee. The efforts of the infrequent tumor subcommittee were primarily directed towards education and development of feasible and novel multidisciplinary single-arm protocols that could maximize the likelihood of success. The major goals of this subcommittee are outlined below. The subcommittee has achieved three of its four goals so far.

12.3 Infrequent Tumor Subcommittee Goals

12.3.1 Tumor Banking Protocol

A tumor banking study (ABTR01B1 study) was opened in 2003 for the collection and storage of pediatric tumors, including rare pediatric tumors. Since its initiation, rare tumors are banked on this protocol and are available to future investigators for study. Formal requests for material must be submitted as part of a scientific proposal and will be reviewed for merit.

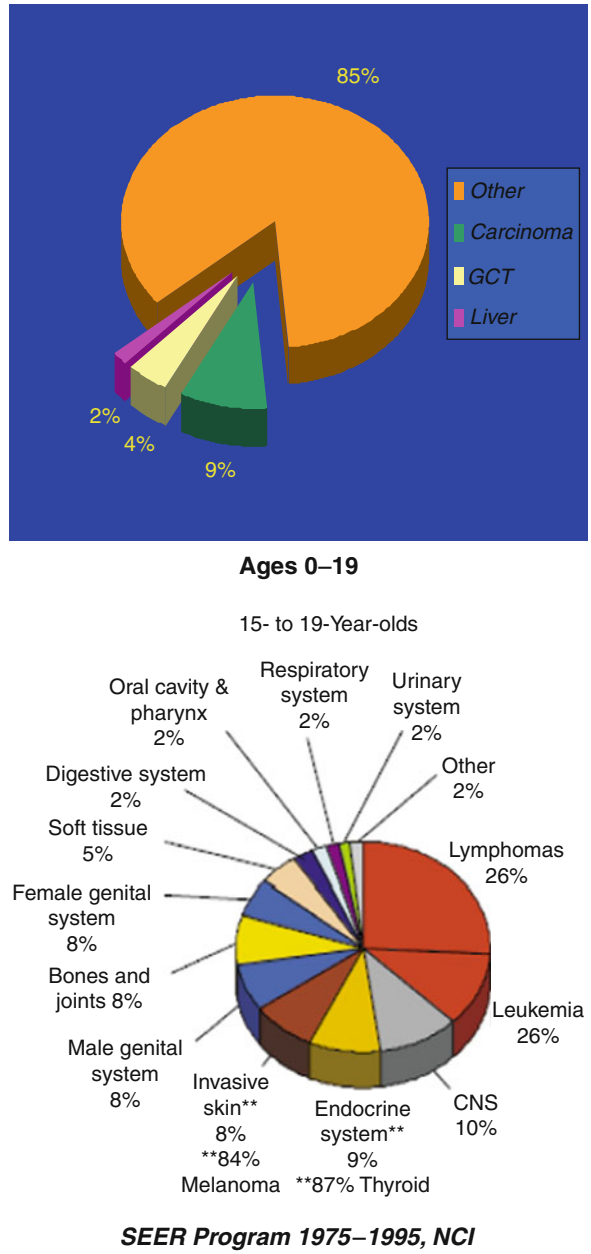

Fig. 12.1 Incidence of rare tumors in children from SEER data 1975–1995

12.3.2 Clinical Trials

The second aim of the group was to open clinical trials for rare tumors in collaboration with international groups. This has been achieved by the opening of an international trial (ARAR0332) which is an ongoing Phase III study for adrenocortical carcinomas being conducted in the United States and Brazil, and by the development of a clinical trial to study the biology and treatment of nasopharyngeal carcinoma (ARAR0331).

12.3.3 Diagnostic and Therapeutic Recommendations

The third major goal of the committee was to develop diagnostic and therapeutic recommendations for select rare tumors, by summarizing current literature reviews. A total of eight rare tumors were identified for the development of guidelines. These included thyroid carcinomas, colorectal carcinoma, melanoma, gastrointestinal stromal tumor, pancreatoblastoma, desmoplastic small round cell tumor, gonadal stromal tumors, and carcinoid tumors. In order to develop the guidelines, a working group was established, which consisted of pediatric oncologists, surgeons and pathologists, and radiation oncologists. For each tumor guideline, one or two investigators were identified with expertise in that tumor type. The investigators produced a preliminary document based on a detailed literature review, summarizing the epidemiology, biology, clinical features, and diagnostic and therapeutic recommendations. The document was then reviewed and revised by senior members of the Rare Tumor Committee. The final guidelines have been submitted for publication, for wide dissemination to pediatric oncologists. The authors of each rare tumor guideline also form a network of experts available to treating clinicians to help with the management of these rare tumors.

12.3.4 Rare Tumor Registry

The final goal of the committee is to develop a rare tumor registry. We are currently working on this initiative and in the future hope to partner with other international rare tumor groups to develop an international registry for rare tumors.

References

Pappo AS, Krailo M, Chen Z, Rodriguez-Galindo C, Reaman G (2010) Infrequent tumor initiative of the children's oncology group: initial lessons learned and their impact on future plans. J Clin Oncol 28(33):5011–5016

Ries LA, Smith MA, Gurney JG (1999) Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. National Cancer Institute, Bethesda, SEER Program Pub. No. 99-4649

The E*X*PeRT Initiative

13

Gianni Bisogno

Working to improve the knowledge and find appropriate treatments for children with rare diseases means to confront with many disadvantages: lack of interest from the scientific, economic, and political community; lack of funds; and lack of colleagues to work with to exchange ideas and projects. Although cancer is a rare disease in children, pediatric oncologists have been able to improve treatment, perform research, raise interest, and find support. Maybe more importantly, the impossibility to perform meaningful studies on the few patients treated in each pediatric oncology center has fostered the search for links and connections with other centers, initially on a national level and subsequently to a more international dimension. Until recently, children suffering from cancers with extremely low incidence have participated in this progress to a far less extent. Therefore, several national groups specifically focussing on rare cancers in childhood have been founded in the new millennium. These initiatives have contributed to increase awareness of the problem of children with very rare tumors, and ultimately lead to the formation in June 2008 of a new cooperative group denominated E*X*PeRT – European Cooperative Study Group for Paediatric Rare Tumors.

The main aim of this group is to empower the research on rare pediatric tumors by promoting collaboration between the founder national groups: Italy, France, United Kingdom, Poland, and Germany. Data exchange, retrospective and prospective studies, harmonized and internationally recognized guidelines, and E*X*PeRT consultation to assist clinical decision and international case registry are the undergoing initiatives. The formation of similar groups in other countries is also expected and supported.

As an initial initiative, the E*X*PeRT group decided to combine the data collected by each national group on some tumor entities included in the list of very rare pediatric tumors. For this purpose, a harmonized core data sheet for uniform documentation of clinical data of children with rare cancers was developed. This data sheet has then be adapted for three retrospective studies focussing on ovarian Sertoli–Leydig cell tumors, pancreatoblastoma, and pleuropulmonary blastoma.

Pancreatoblastoma (PBL) was selected as the first tumor type to be analyzed and was the subject of the first publication: in a 10-year period, 20 cases only were collected from Italy, France, United Kingdom, Poland, and Germany. This suggests that even at a European level, it is too rare to allow the recruitment of sufficient number of cases to conduct clinical trials leading to evidence-based treatment guidelines. Nevertheless, the E*X*PeRT group would propose a sort of standard approach for PBL, including a surgical staging system, an initial conservative surgical approach, chemotherapy according to PLADO regimen, and a post-chemotherapy aggressive surgery, on both primary tumor and metastases, when present.

Additional studies included 42 Sertoli–Leydig cell tumors. Thus, they represent the largest series of these tumors reported to date. Both provide significant new information, in particular, with regard to the further development of therapeutic strategies in these rare

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tumors. In 2010, the first results have been presented at the meeting of the International Society of Pediatric Oncology (SIOP), and publication of these studies is expected in 2011.

To perform research on rare tumors requires an enormous and prolonged effort as results may be visible only in the long term. We do not expect that E*X*PeRT will radically change the scenario, but at least it will be able to bring this problem to the attention of the medical community. Remarkably, despite potentially heterogeneous diagnostic and therapeutic strategies used in the different national groups, such studies may provide new options to promote our knowledge of rare cancers and to advance clinical management. The abovementioned small studies, however, demonstrate that international cooperation in very rare tumors is feasible and support the benefit of the foundation of the E*X*PeRT group (Table 13.1). International cooperative studies on rare entities may thus significantly help in advancing our clinical understanding and in improving our clinical care in these tumors. Further steps are needed to facilitate the collection of larger numbers of cases by creating a prospective international registry and to set up a biorepository to stimulate biological studies to improve our understanding of the molecular genetic basis and the natural history of specific rare tumors.

Table 13.1 Founding members and "core group" of E*X*PeRT

National group	Coordinator	Clinical speciality
TREP, Italy	Gianni Bisogno	Pediatric oncology
	Giovanni Cecchetto	Pediatric surgery
	Andrea Ferrari	Pediatric oncology
UKCCSG, UK	Bernadette Brennan	Pediatric oncology
PPGGL, Poland	Ewa Bien	Pediatric oncology
	Jan Godzinski	Pediatric surgery
	Teresa Stachowicz-Stenzel	Pediatric oncology
France	Daniel Orbach	Pediatric oncology
	Yves Reguerre	Pediatric oncology
STEP, Germany	Ines Brecht	Pediatric oncology
	Dominik T. Schneider	Pediatric oncology

We hope that with E*X*PeRT, the enormous disadvantage of rare diseases may be transformed in the advantage that doctors and scientists recognize they are forced to collaborate on a large international level. This will hopefully improve the quality of research and the treatment results for children that have been, until recent years, partially neglected.

Part IV

Information and Resources for Clinicians and Patients with Rare Tumors

Internet Resources

14

Ines B. Brecht and Sonja Offenmüller

Contents

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14.1 Introduction

Information on cancer is available through books, the Internet, contributions on congresses and meetings, and through working groups of the National Cancer Societies. In the specific situation of rare pediatric tumors, it is not easy to get reliable, practical, and precise information on diagnosis and management. In many situations, it will be necessary for health care providers to contact the coordinators of the rare pediatric tumor working groups in order to use their expertise and interdisciplinary network for specific questions (see Chapters 7–12). Anyway, the Internet provides a great insight to patients as well as to attending physicians into the situation of cancer research today. It offers a wide range of specific information websites about different malignancies, current standards of research and experts and helping support for patients and affected family members. Also, in the case of rare tumors, the Internet can give first information on tumor entities and the structure and functioning of the rare tumor networks nationally and worldwide.

We want to mention some information resources in the Internet, which might be helpful for the care of rare pediatric tumors.

14.2 International Websites

14.2.1 Medline®

http://www.ncbi.nlm.nih.gov/pubmed/

The US National Library Medicine (NLM) allows free access to MEDLINE®, a bibliographic database containing over 12 million references to articles

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published in over 4,000 medical journals worldwide since 1966. It was developed by the National Center for Biotechnology Information at the NLM and covers all aspects of the life sciences and medicine. By searching MEDLINE®, physicians can find journal articles – including abstracts in most cases and free full articles in some cases – on rare pediatric tumors. So far, experience in the field of rare pediatric tumors very much relies on original reports, which can be found via MEDLINE®. PubMed is also linked to molecular biology databases and to PubMed Central, an electronic archive of life sciences journal literature.

14.2.2 Orphanet

http://www.orpha.net

This website is exclusively dedicated to rare diseases and orphan drugs. It is provided in several languages (in English, German, French, Spanish, and Italian) and constitutes an international collaboration of around 40 European countries. Under the coordination of a French team, experts from every participating country are in charge of collecting information about clinical services, research activities, and patient organizations at the country level. The website offers a comprehensive database for physicians and patients on rare diseases, orphan drugs, expert centers, diagnostic tests, research trials, registries, biobanks, and patient organizations. Detailed information on characteristics of the disease, latest articles, expert centers and patient organizations, clinical trials, and current research can be retrieved through a search machine as well as an encyclopedia. While the website provides resources on rare tumor syndromes and malignancies rarely found in adults, information about rare pediatric tumors themselves is still scarce.

14.2.3 International Society of Paediatric Oncology (SIOP)

http://www.siop.nl/

The International Society of Paediatric Oncology (SIOP) was established in Switzerland in the late 1960s with its first annual meeting in Madrid in 1969. Since then, the members (physicians and scientists) have formed a worldwide organization, which aims to have over 50% of all countries and of all pediatric oncologists represented in SIOP. Worldwide standards of pediatric oncological treatment and knowledge shall be provided. Thus, the annual congress is the most important event of the organization, where new research and current standards in pediatric oncology are presented. This information is further published in the official journal of SIOP "Pediatric Blood and Cancer" (PBC), as well as on the website as "educational book" or "keynote lectures."

14.3 National Websites

14.3.1 The US National Cancer Institute's (NCI) Website

http://www.cancer.gov

The US Nation Cancer Institute's (NCI) website provides comprehensive research-based information for patients and their families, health professionals, and cancer researchers. The contents are written by experts and updated regularly, therefore based on current standards of care and the latest research. Extensive information on diagnosis and treatment of childhood and adult-type tumors, on clinical trials, genetics, and statistics (Surveillance, Epidemiology, and End Results database – SEER) can be found. There is also a section on cancer occurring in adolescents and young adults as well as unusual cancers occurring in childhood.

14.3.2 The US National Cancer Institute PDQ Cancer Information Site

http://www.cancer.gov/cancertopics/PDQ

This specific site within the NCI website provides specific information on the treatment of cancer in children, adolescents, and adults. Adult and pediatric treatment summaries are available for both patients and health professionals. This site is constantly updated by active editorial boards.

14.3.3 The US Children's Oncology Group

http://www.childrensoncologygroup.org

The Children's Oncology Group (COG) is based in the USA and Canada but also includes institutions in Australia and Europe. The CureSearch website has both a members' only site as well as information for patients and physicians, providing valuable information for the treatment of pediatric cancers.

14.3.4 The UK Children's Cancer and Leukaemia Group

http://www.cclg.org.uk/index.php

The Children's Cancer and Leukaemia Group (CCLG) was founded in 2006, when the UK Children's Cancer Study Group and the UK Childhood Leukaemia Working Party were merged. They had been existing individually since the 1970s. Comprehensive information resources for patients and health professionals are provided on management, clinical trials, and support. Specific information and guidelines for rare tumor entities can be found (Rare tumor working group of CCLG).

14.3.5 The German Society for Paediatric Oncology and Haematology (GPOH)

http://www.kinderkrebsinfo.de

The members of the German Society for Paediatric Oncology and Haematology (GPOH) are physicians, researchers, nurses, psychologists, and other health professionals from Germany, Austria, and Switzerland, working closely together in order to provide best care for children and young adults with malignancies. The website is available in German and English and provides general information on childhood cancer and blood disorders for health care providers and patients as well as specific information on latest diagnostic and treatment standards, research activities, clinical trials, etc. So far, only few rare pediatric tumors are described, but information on working groups is given. The website is still in construction and therefore permanently improved. It offers current information on research and publications as well as a detailed description of the organization and task fields of the GPOH.

14.3.6 The Italian TREP Project (Tumori Rari in Età Pediatrica [Rare Tumors in Pediatric Age])

http://trepproject.org

The website of the Italian TREP project (Italian rare pediatric tumor group) includes information (mainly in Italian language) on the structure of the group, the centers and members involved, the projects and the activity, news, meetings, and publications. There is an additional "members area" with diagnostic and treatment guidelines for each tumor type. The TREP project is a working group of the Italian pediatric oncology association (Associazione Italiana Ematologia Oncologia Pediatrica – AIEOP).

http://www.aieop.org

14.3.7 La Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent (SFCE)

http://sfce1.sfpediatrie.com/

http://www.igr.fr/fr/page/les-tumeurs-rares_125

The French Society for Pediatric Oncology and Hematology (Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent (SFCE)) was founded in 2002 as a reunion of the Societies for Pediatric Oncology and Leukemia. Information is provided in French. There are some recommendations for rare pediatric tumors, but for access to detailed guidelines, it is necessary to be a member of the French SFCE.

14.4 Cancer Registries

14.4.1 US Surveillance, Epidemiology, and End Results Database (SEER)

http://seer.cancer.gov/

The Surveillance, Epidemiology, and End Results (SEER) Program is a primary source for cancer statistics in the USA, collecting incidence, prevalence, and survival data of representing areas of the USA (28% of the US population). Visitors of the website can get detailed data either through prepared cancer statistics reviews, "fast stats," which enables the user to produce his own graphs for different epidemiological data, or through retrieving SEER data and analyzing them for scientific questions. Analyses of data from SEER are of utmost importance for the research in the field of rare tumors as few publications on the epidemiology of these entities are available so far.

14.4.2 Automated Childhood Cancer Information System (ACCIS)

http://www-dep.iarc.fr/accis.htm

The Automated Childhood Cancer Information System (ACCIS) has the goal to collect, present,

interpret, and disseminate data on childhood cancer in Europe. The project is funded by the European Commission. It collected about 160,000 records on childhood and adolescent cancer cases registered over the last 30 years in 78 European population-based cancer registries. The ACCIS Scientific Committee insures comparability of the individual datasets presented in a set of standard tables and comments on differences in data collection and processing. Like practiced at the SEER registry, the database is distributed to all scientists who want to work with the data.

14.4.3 German Childhood Cancer Registry

http://www.kinderkrebsregister.de/

The website presents the work and organization of the German Childhood Cancer Registry, providing epidemiology data for physicians. Thus, this database (in German or English available) is a combination of population-based and hospital-based registry and gives a detailed insight into the number of patients suffering from cancer since 1980, which adds ups to 44,866 registered patients (until 2008). Research projects, cooperation projects, as well as specific publications are available, e.g., the annual reports of the organization.

14.5 Patient's Website

Most of the websites described above given information for patients and health professionals in separate sections. Anyway, cancer support organizations are especially focused on providing information for patients.

14.5.1 Macmillan Cancer Support

http://www.macmillan.org.uk

The Macmillan Cancer Support is a charity organization, which cares not only about rare tumors or tumors in childhood; it is the biggest cancer foundation in the UK, dedicated to all types of cancer in all ages. The goal of the foundation is to help patients and affected people on a psychological, informational, and financial level. The website gives information in the form of articles and other publications; patients can easily achieve an insight into cancer types, treatments, risk factors, and causes – including rare pediatric tumors. Macmillan gives therefore a wide range of contact addresses to health and social care professionals. There is a hotline, which can be used to talk to a Macmillan specialist; an online community, which enables contact to affected people; as well as addresses of information centers, support groups, or courses to improve knowledge and understanding. Macmillan finally cares about financial miseries as well, trying to support patients and families who are not able to fund the treatment of cancer.

14.5.2 Kinderkrebsstiftung

http://www.kinderkrebsstiftung.de

Starting as a working group of parents whose children suffered from cancer, this organization is now an official foundation in Bonn, working in close collaboration with the GPOH (German Society of Paediatric Oncology and Haematology) and other international foundations and organizations regarding cancer in childhood. Their work aims to help and support affected people. Therefore, the direct way is used by advising and informing patients as well as by financial support in special situations. Patients and families can donate money for the deserving poor or receive financial support. The foundation also supports research projects. The website gives short information on malignancies, diagnosis, and treatment referring to contents of kinderkrebsinfo.de.

14.6 Other Useful Websites

14.6.1 The Familial Cancer Database (FaCD)

http://www.familialcancerdatabase.nl/

This website has the goal to "assist clinicians in making a genetic differential diagnosis in cancer patients, as well as in becoming aware of the tumor spectrum associated with hereditary disorders that have already been diagnosed in their patients." The software connects tumor features and other characteristics of the patient and his/her family with over 500 hereditary disorders associated with increased cancer risk. There is a link to OMIM®, Online Mendelian Inheritance in Man®, and other important websites. The focus of the synopsis lies on phenotype, and there is an estimation of cancer risk.

A document with suggestions on how to search the database and interpret its results is available in the "Find Syndromes" screen under the "How to search for syndromes" button. We advise users to read it.

14.6.2 MD Anderson Cancer Center

http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-topics/prevention-and-screening/hereditary-cancer-syndromes/index.html

An overview on hereditary cancer syndromes is given, and PDF files for the most important syndromes provided. Some information on the practical approach is provided.

Part V

Rare Tumors of the Head and Neck

Differential Diagnosis of Head and Neck Tumors

15

Jan Godzinski and Ines B. Brecht

Content

Head and neck pathologies are frequent in childhood but rarely have malignant origin. Traumatic lesions, inflammatory enlargement of the lymph nodes, congenital malformations, cysts, hemangioma, lymphangioma, vascular malformations, and even infectious diseases may mimic malignant conditions. A classical diagnostic workup is well applicable to differentiate between those conditions.

Carefully collected medical history, precise physical examination, and correctly selected imaging and laboratory tests help in preselecting the patients with justified suspicion of malignancy. The flowchart diagram (Fig. 15.1) describes the characteristics of different head and neck masses. Signs and symptoms of malignant head and neck tumors might seem more or less harmless like an enlarged lymph node or unusual swelling, ear ache, bleeding, a sore throat, or difficulties swallowing or breathing. Patients suspicious to have a malignant condition require further detailed imaging and microscopic confirmation. A biopsy should be performed or – in case of small size and favorable localization – a primary excision of the lesion.

Figures 15.2–15.4 show the distribution of malignant head and neck tumors in children and adolescents. Rhabdomyosarcomas and thyroid carcinomas are most often seen, followed by carcinomas of the salivary gland and nasopharyngeal carcinomas. Melanoma of the skin is excluded from this analysis. The following unusual pediatric head and neck cancers are discussed in the following chapter, "head and neck tumors": nasopharyngeal carcinoma, esthesioneuroblastoma, thyroid tumors, oral cancer, salivary gland cancer, and laryngeal carcinoma.

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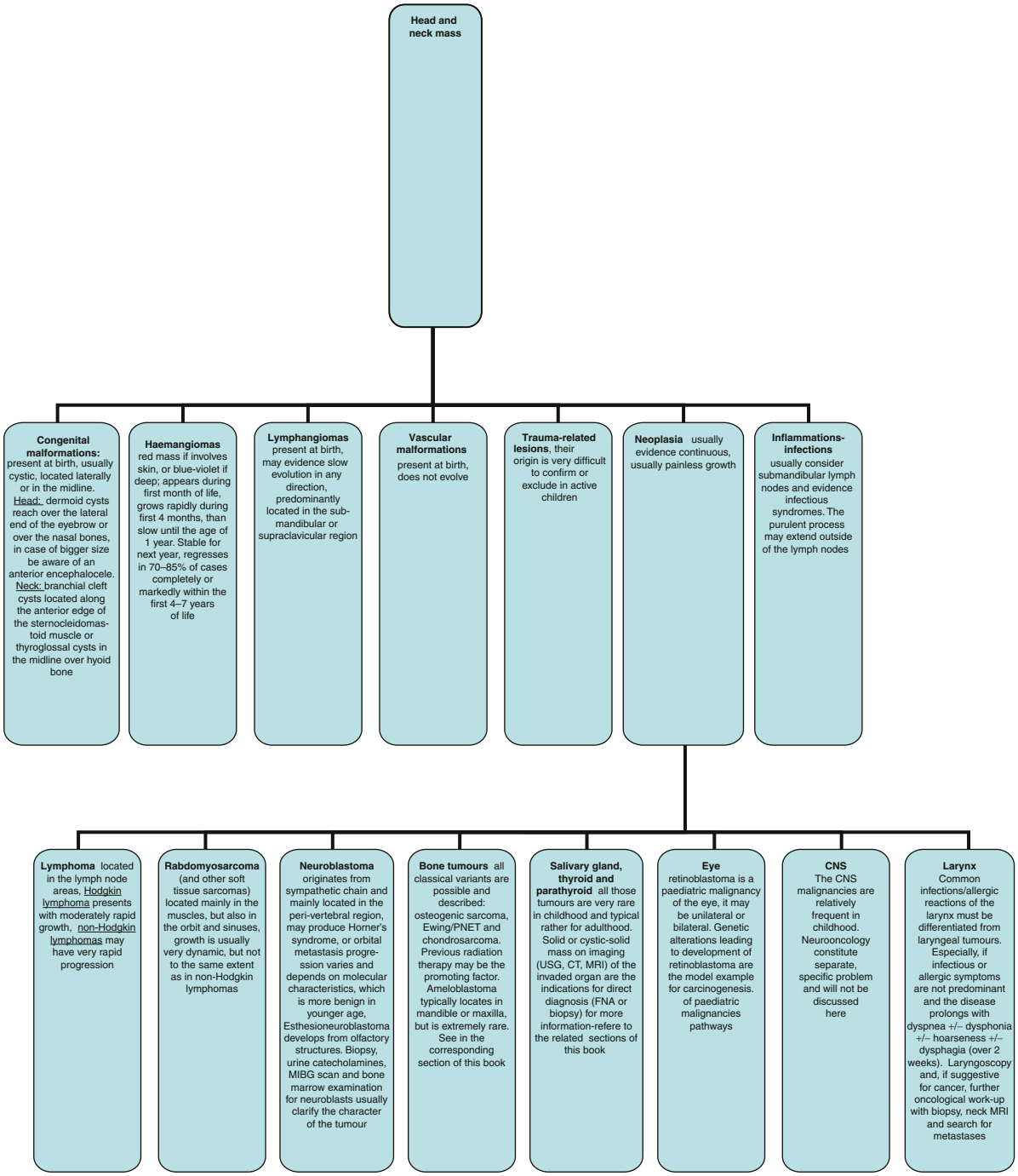

Fig. 15.1 Characteristics of commonly observed head and neck masses and rare malignant entities (Courtesy of Strong and Jako 1972)

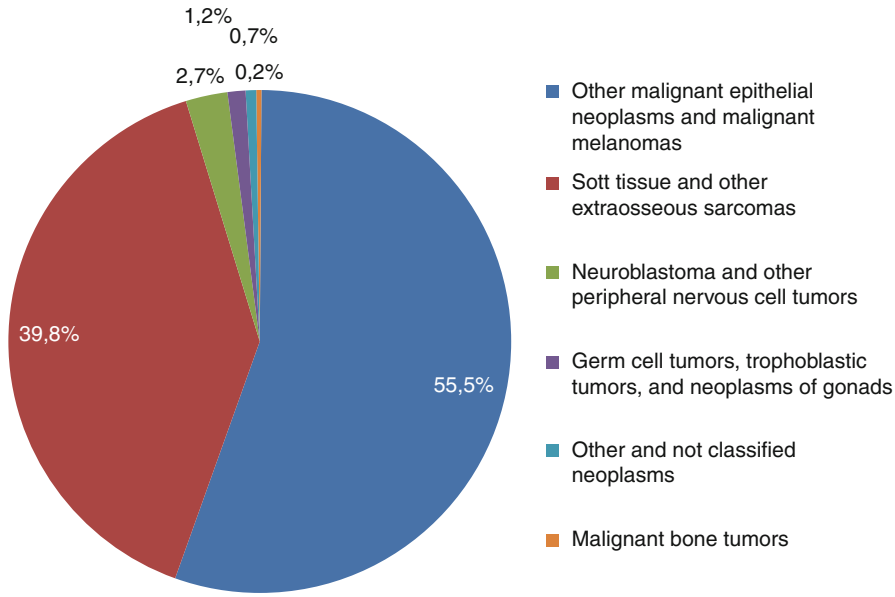

Fig. 15.2 Distribution of head and neck tumors by ICCC-3 category in children under the age of 15 years. Data from the United States Surveillance and End Results Registry (SEER), 1973 to 2004 (*Note*: Melanoma of the skin of head and neck are not included in the analysis)

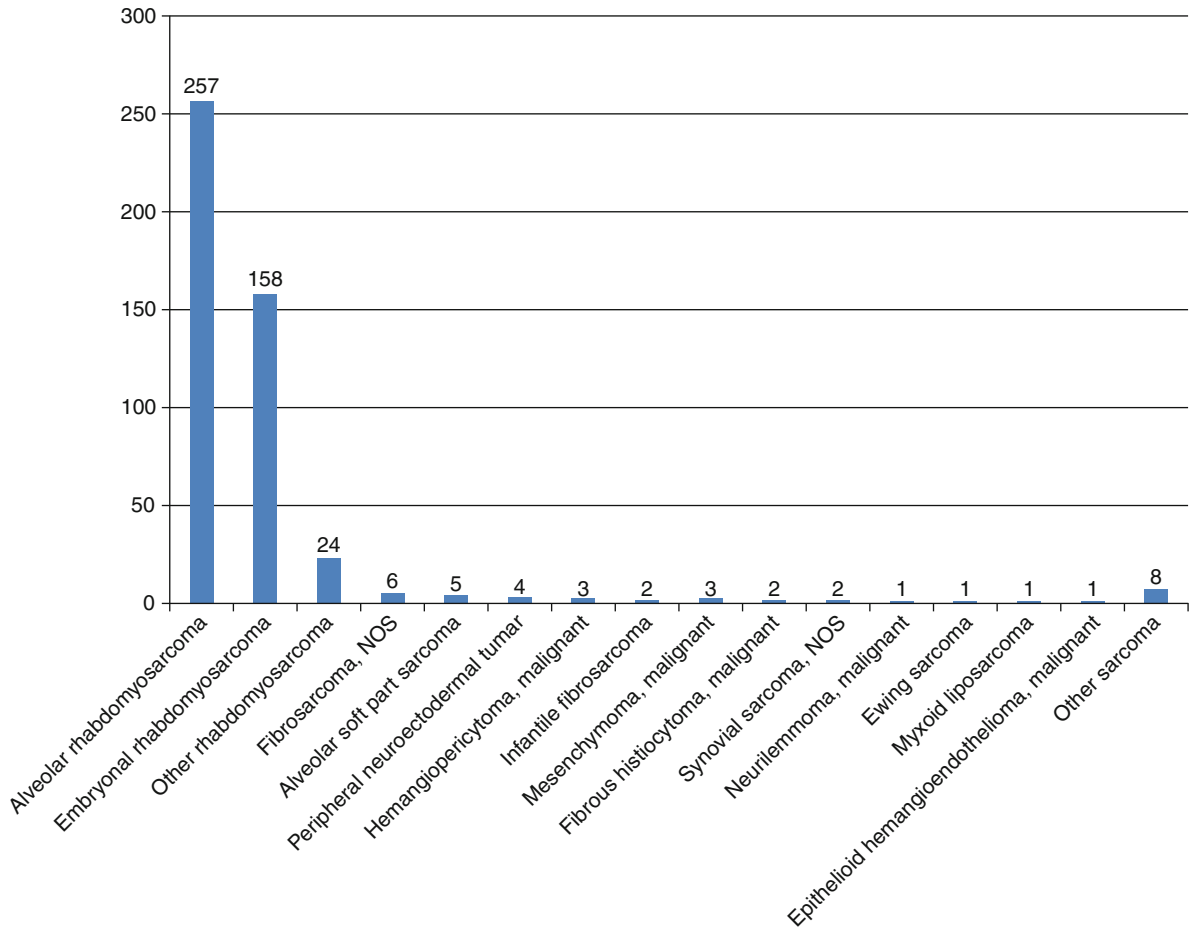

Fig. 15.3 Distribution of soft tissue sarcomas of head and neck tumors by ICD-3 code in children under the age of 15 years. Data from the United States Surveillance and End Results Registry (SEER), 1973 to 2004

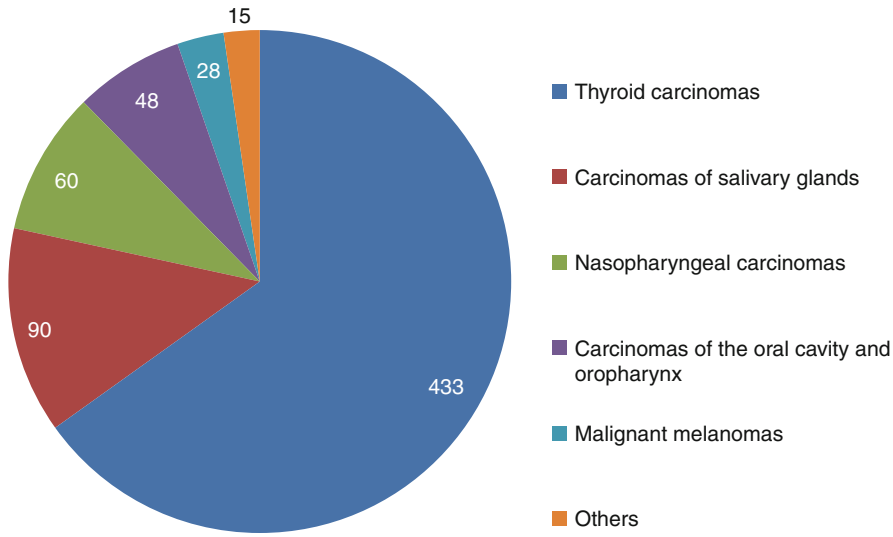

Fig. 15.4 Distribution of "other malignant epithelial neoplasms and malignant melanomas" of head and neck by ICD-3 code in children under the age of 15 years. Data from the United States Surveillance and End Results Registry (SEER), 1973 to 2004 (*Note*: Melanoma of the skin of head and neck are not included in the analysis)

References

Bhandarwar AH, Utture SS, Shaikh A et al (2008) A rare case report of parotid haemangioma in a child treated by sclerotherapy using bleomycin. Bombay Hosp J 50(4):672–675

Ferlito A, Renaldo A, Marioni G (1999) Laryngeal malignant neoplasms in children and adolescents. Int J Pediatr Otorhinolaryngol 49(1):1–14

Fitzgerald R, Koenigs I (2009) Skull. In: Zachariou Z (ed) Pediatric surgery digest. Springer, Berlin/Heidelberg, pp 183–196

Fitzgerald R, Godzinski J, Gentil Martins A et al (2009) Pediatric surgical oncology. In: Zachariou Z (ed) Pediatric surgery digest. Springer, Berlin/Heidelberg, pp 541–604

Guzzo M, Ferrari A, Marcon I et al (2006) Salivary gland neoplasms in children: the experience of the Istituto Nazionale Tumori of Milan. Pediatr Blood Cancer 47(6):806–810

Kato MA, Flamant F, Lacombe MJ et al (1991) Rhabdomyosarcoma of the larynx in children. Med Pediatr Oncol 19(2):110–114

Kessler A, Dominiques FZ (1986) Ameloblastoma in childhood. J Oral Maxillofac Surg 44:609

Nikaghlagh S, Saki N, Mostofi NE et al (2007) Rhabdomyosarcoma of the larynx. Pak J Med Sci 23(2):280–282

Raine P (2009a) Face. In: Zachariou Z (ed) Pediatric surgery digest. Springer, Berlin/Heidelberg, pp 203–214

Raine P (2009b) Neck. In: Zachariou Z (ed) Pediatric surgery digest. Springer, Berlin/Heidelberg, pp 215–226

Sessions RB, Harrison LB, Hong WK (1993a) Tumours of the larynx and hypopharynx. In: DeVitta V, Hellman S, Rosenberg SA (eds) Cancer. Principles & practice of oncology. Lippincott, Philadelphia

Sessions RB, Harrison LB, Hong WK (1993b) Tumors of the salivary glands and paragangliomas. In: DeVitta V, Hellman S, Rosenberg SA (eds) Cancer. Principles & practice of oncology. Lippincott, Philadelphia

Strong MS, Jako GJ (1972) Laser surgery in the larynx. Early clinical experience with continuous CO2 laser. Ann Otol Rhinol Laryngol 81:791–798

Thyroid Carcinomas

16

Maura Massimino, Antje Redlich, Paola Collini, and Peter Vorwerk

Contents

16.1 Introduction

Thyroid cancers account for the most frequent tumors of endocrine glands in childhood and adolescence; however, these solid tumors are rare in this population. Currently, about 10% of all thyroid cancers occur in patients under 21 years of age (Buckwalter et al. 1981). The annual incidence as derived from the Surveillance, Epidemiology, and End Results (SEER) registry is 0.54 cases per 100,000 persons (Hogan et al. 2009).

The classification of thyroid carcinomas follows the World Health Organization (WHO) Classification of Tumours edited in 2004, which considers both pathology and genetics in defining the histotypes (Table 16.1) (Rosai et al. 2011; DeLellis et al. 2004a). In childhood, the vast majority of follicular cell–derived thyroid cancers are differentiated thyroid carcinomas, i.e., papillary and follicular carcinomas. Both poorly differentiated and undifferentiated (anaplastic) carcinomas are practically absent in this age and are not discussed in this chapter (De Keyser and Van Herle 1985).

16.2 Differentiated Thyroid Carcinoma

16.2.1 Epidemiology and Etiology

Differentiated thyroid cancer (DTC), which derives from follicular epithelial cells, includes papillary and follicular carcinomas and accounts for more than 90% of thyroid cancer in childhood (Danese et al. 1997). Among DTC, papillary thyroid carcinoma (PTC) is the most common type, with ionizing radiations appearing to be an important causal factor (Ron et al. 1989). Accordingly, a steep rise in the incidence of PTC was

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Table 16.1 Classification of thyroid carcinoma

1. Malignant tumors of follicular cells
   - 1.1 Differentiated thyroid carcinoma (DTC)
     - 1.1.1 Papillary thyroid carcinoma (PTC)
     - 1.1.2 NOS
       - 1.1.2.1 Histopathological variants
         - 1.1.2.1.1 Follicular variant
         - 1.1.2.1.2 Macrofollicular variant
         - 1.1.2.1.3 Oncocytic variant
         - 1.1.2.1.4 Clear cell variant
         - 1.1.2.1.5 Diffuse sclerosing variant
         - 1.1.2.1.6 Tall cell variant
         - 1.1.2.1.7 Columnar cell variant
         - 1.1.2.1.8 Solid variant
         - 1.1.2.1.9 Cribriform carcinoma PTC with focal insular component
         - 1.1.2.1.10 PTC with squamous cell or mucoepidermoid carcinoma
         - 1.1.2.1.11 PTC with spindle and giant cell carcinoma
         - 1.1.2.1.12 Combined papillary and medullary carcinoma
         - 1.1.2.1.13 Papillary microcarcinomas
     - 1.1.3 Follicular thyroid carcinoma (FTC)
     - 1.1.4 Minimally invasive (encapsulated)
     - 1.1.5 NOS
       - 1.1.5.1 Oncocytic variant
       - 1.1.5.2 Clear cell variant
       - 1.1.5.3 Widely invasive
       - 1.1.5.4 NOS
       - 1.1.5.5 Oncocytic variant
       - 1.1.5.6 Clear cell variant
   - 1.2 Poorly differentiated carcinoma (PDC)
   - 1.3 Undifferentiated (anaplastic) carcinoma
2. Malignant tumors of C cells
   - 2.1 Medullary thyroid carcinoma (MTC)

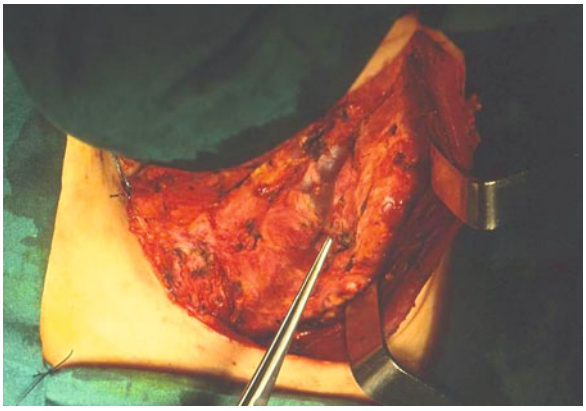

Fig. 16.1 Early operatory field showing secondary adenopathies

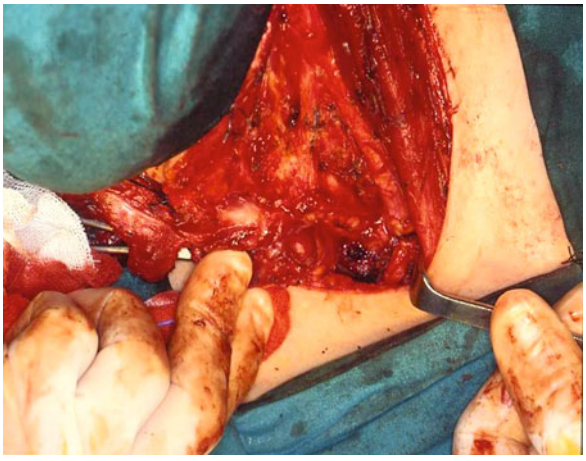

Fig. 16.2 During recurrent node resections

observed in the young population following the 1986 Chernobyl nuclear accident (Kazakov et al. 1992; Mettler et al. 1992). Also, children treated with radiation therapy on the neck for malignant diseases, such as Hodgkin lymphoma or medulloblastoma, or in the past for benign pathologies such as thymic hyperplasia, are at risk for subsequent PTC (Bhatia et al. 2003). Other risk factors are Hashimoto thyroiditis or genetic syndromes, such as Gardner's syndrome (Bell and Mazzaferri 1993; Okayasu et al. 1995; Ott et al. 1985). The preponderance of affected females throughout the literature is likely to be related to estrogen sensitivity of the thyroid gland (Hogan et al. 2009; Farahati et al. 1998; dos Santos Silva and Swerdlow 1993). In fact, in prepubertal children, the gender influence is not that clearly detectable (Jarzab et al. 2005). Follicular thyroid carcinoma (FTC) are of the minimally invasive type, being the widely invasive type exceptional (Figs. 16.1–16.3).

16.2.2 Clinical Presentation and Diagnosis

Among DTC, PTC and FTC show a different presentation and biologic behavior. Both of them can present with a thyroid mass, and lung and bone metastases are possible. Nodal metastases are very frequent in PTC but practically absent in FTC.

Along these lines, children with DTC most commonly present with asymptomatic thyroid mass or

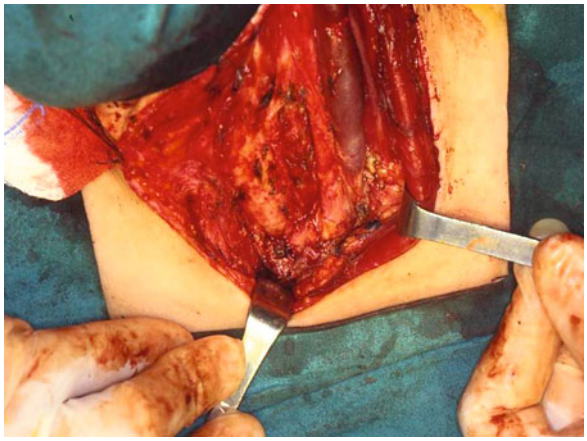

Fig. 16.3 Final result

palpable cervical lymphadenopathy (Danese et al. 1997; Chen et al. 1994; Chaukar et al. 2005). Hoarseness, dysphagia, and bronchial obstruction are not frequently found as initial symptoms.

Differentiating DTC from benign thyroid nodules challenges pediatricians, pediatric endocrinologists, and pediatric oncologists. Thyroid nodules are uncommon in childhood, affecting 0.5–0.7% of children and adolescents (Aghini-Lombardi et al. 1999; Liesenkotter et al. 1997). Since the frequency of malignancy in pediatric thyroid nodules is not quite clear, a carcinoma has to be ruled out as reliable in any case (Yip et al. 1994). In a meta-analysis, the mean incidence of DTC in pediatric thyroid nodules which were operated on was 26.4% (Niedziela 2006). Any nodule discovered in this age group should therefore be viewed with suspicion, and the diagnostic approach should be more extensive than in adults.

In the presence of a cervical mass, clinical assessment of the site of the nodule (thyroid vs node vs other), its characteristics (size, consistency, and mobility), and laryngeal or esophageal involvement (dysphonia and dysphagia) should be checked performed. Fixation of the mass to adjacent structures and lymphadenopathy are suspicious of malignancy (Lugo-Vicente and Ortiz 1998; Lassaletta et al. 1997).

In laboratory examinations, no preoperative marker is able to distinguish DTC from benign nodules. Nevertheless, laboratory evaluation of thyroid function and serum thyroglobulin is useful. Thyroglobulin is used to detect recurrence of DTC after total thyroidectomy and ablative radioiodine therapy (Herle and Uller 1975; Ng Tang Fui et al. 1979).

Ultrasonography characterizes size and appearance of the gland and the nodules (see Figs. 16.4 and 16.5). The only reliable indicators for malignancy are invasive growth into surrounding tissue and metastases to cervical lymph nodes (Hegedus and Karstrup 1998).

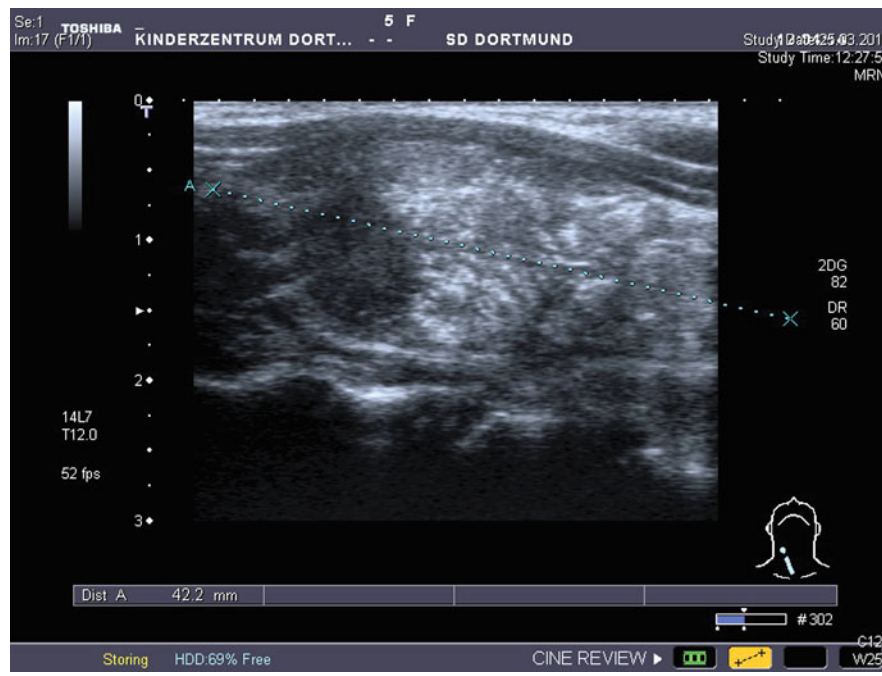

Fig. 16.4 Ultrasound of a thyroid carcinoma in right lobe of the thyroid

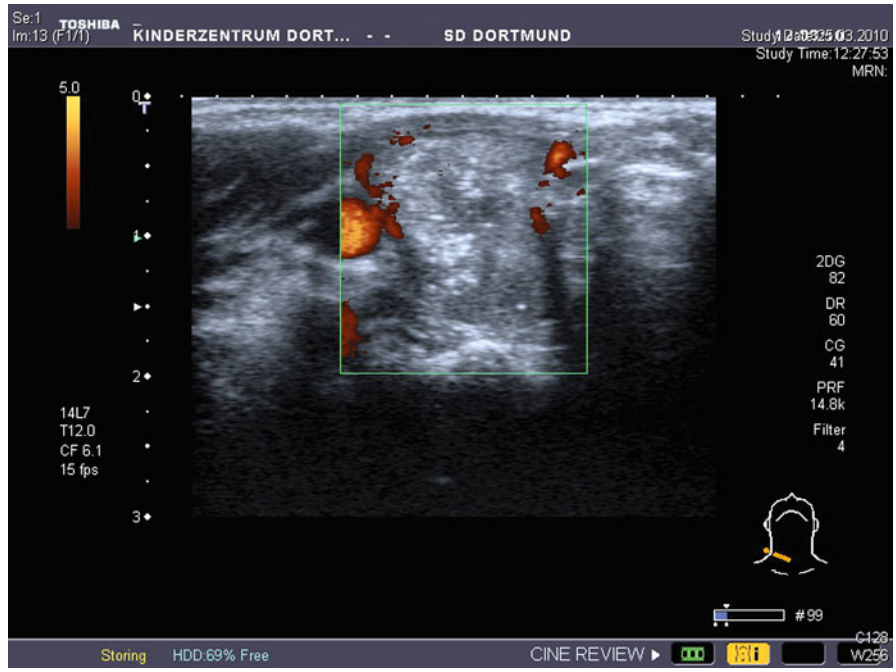

Fig. 16.5 Ultrasound of lymph node involvement of patient with thyroid carcinoma

Other sonographic findings such as hypoechogenicity, solid composition, irregular margins, or microcalcifications are associated with an increased risk of malignancy but usually can not distinguish benign from malignant nodules accurately.

In adults, numerous reports confirm that the introduction of fine-needle aspiration biopsy (FNAB) reduced thyroid surgery and increased the yield of carcinoma in patients who underwent surgery dramatically (Gharib and Goellner 1993). In young patients, FNAB has not been utilized extensively, and the scanty studies reported are often in disagreement. Nevertheless, a meta-analysis certified FNAB as a sensitive diagnostic test and a useful tool in diagnosing malignancy in pediatric thyroid nodules (Stevens et al. 2009). The procedure should only be performed by experienced physicians and cytologists.

16.2.3 Special Considerations

Several studies have shown that DTC in pediatric patients differs from that in adults with respect to its presentation and outcome (Table 16.2).

The malignant disease in childhood is associated with more locally aggressive behavior and more frequent distant metastases than its adult counterpart (Zimmerman et al. 1988; Jarzab and Handkiewicz-Junak 2007; Schlumberger et al. 1987). As the thyroid gland is smaller in children than in adults, earlier involvement of the thyroid capsule and the surrounding tissue of the neck is possible (Farahati et al. 1999). Recurrence rates tend to be higher in the pediatric population, but nevertheless, cause-specific mortality remains low.

16.2.4 Pathology

Nonmedullary, follicular-derived thyroid carcinomas, encompassing papillary thyroid carcinomas (PTC), follicular thyroid carcinomas (FTC), poorly differentiated carcinomas (PDC), and undifferentiated (anaplastic) carcinomas, represent biologically and genetically different and distinct entities (WHO, Collini et al. 2006a).

While PTC are characterized by a prevalent lymphatic spread, FTC follows a vascular way of diffusion. PTC show a high tendency to intrathyroidal microscopic pluricentricity, intrathyroidal and nodal microscopic lymphatic diffusion, infiltration beyond the thyroid capsule into the soft tissue of the neck, and

Table 16.2 Differentiated thyroid cancer: differences in children and adults

	Children	Adults
Annual incidence (Hogan et al. 2009; Wiersinga 2001)	0.2–2:1,000,000	50–100:1,000,000
Staging at presentation		
Extrathyroidal tumor spread into the soft tissue of the neck (pT4)	52%	15% (low-risk variants) 45% (high-risk variants)
Lymph node metastases (Zimmerman et al. 1988; Farahati et al. 1997)	40–70% (–90%)	30–73%
Distant metastases at onset (Schlumberger et al. 1987; Ruegemer et al. 1988)	12–20% (lung, miliar; bone)	2–10% (lung; rarely bone)
Histology		
Histological subtype (Newman et al. 1998; Welch Dinauer et al. 1998)	PTC 80–90% (low-risk variants)	PTC 80% (also high-risk variants)
Multifocality (Spinelli et al. 2004)	50–80%	30–60%
Size (Wiersinga 2001; Chow et al. 2004; Miccoli et al. 2008)	Larger	Smaller
Outcome		
Event-free survival (5 years) (Jarzab and Handkiewicz-Junak 2007)	60%	80%
Overall survival (Jarzab and Handkiewicz-Junak 2007; Showalter et al. 2008; Parisi and Mankoff 2007)	95–100%	90%

presence of nodal and distant metastases mainly in lungs. FTC are characterized by vascular invasion, distant metastases in bone and lungs, and absence of tendency to invade soft tissue of the neck or nodal metastases (DeLellis et al. 2004b). Genetically, PTC show involvement of RET, TRK, and BRAF, whereas in FTC, RAS mutations are present (DeLellis et al. 2004b). PDC are high-risk tumors that show the biological characteristics of both PTC and FTC and can arise de novo or as progression of malignancy in PTC or FTC (DeLellis et al. 2004b). As with the adult disease, follicular-derived thyroid carcinomas can be divided into low- and high-risk histotypes and variants on the basis of overall survival (OS). In the low-risk group, the vast majority of PTC and the minimally invasive (encapsulated) FTC (MIFTC) with only capsular and/or minimal vascular invasion are included. In the high-risk group, the PTC of the tall cell, columnar cell, and high-risk variants; the MIFC with extensive vascular invasion; and the widely invasive FTC, PDC, and undifferentiated (anaplastic) carcinomas are included (DeLellis et al. 2004b; Collini et al. 2004). The vast majority of pediatric thyroid carcinomas are PTC. In these ages, FTC are exceptional and occur as low-risk MIFC only. PDC are exceptional. Many thyroid carcinomas which have been diagnosed as FTC or PDC (i.e., insular carcinomas, solid/trabecular FTC, and moderately differentiated FTC) in the past are indeed low-risk PTC of the follicular, encapsulated follicular, or solid/trabecular variants (DeLellis et al. 2004b). In childhood, high-risk histotypes of thyroid carcinomas such as widely invasive FTC and undifferentiated (anaplastic) carcinomas are practically absent.

16.2.5 Therapy

The management strategies for differentiated thyroid carcinoma in children remain to be debated. In general, the radical approach utilizing radical surgery (thyroidectomy plus lymph node dissection) followed by radioiodine therapy and TSH suppression aims for control of both macro- and microscopic diseases. This strategy has been adopted from corresponding trials in adult patients. However, considering potential long-term sequelae of this treatment, a more conservative approach might also be considered for selected patients. This strategy aims for control of only macroscopic disease with limited surgery (hemithyroidectomy plus limited neck dissection) without radiotherapy but always followed by TSH suppression. In the perspective of the excellent (almost 100%) overall survival with both approaches, these two options have to be carefully weighed in each patient, since no prospective

Table 16.3 Comparison between the radical versus conservative approach in thyroid carcinoma of children and adolescents

Radical (same as for adults)	Therapeutic approach	Conservative [tailored for selected pediatric patients (tumors limited to one lobe, ± clinical evidence of monolateral N)]
Initial eradication of all clinical and subclinical neoplastic foci (at T, N, and M)	Strategy	Removal only of grossly detectable disease, without searching for microscopic disease after surgery
Improve progression-free survival by detecting and treating all tumor cells, and preventing any dedifferentiation of occult neoplastic micro-foci	Aims	Contain treatment morbidity, without jeopardizing the zero mortality rate (the risk of tumor dedifferentiation from microscopic disease seems to be merely theoretical in children)
Total thyroidectomy (regardless of the tumor extent)	Thyroid resection	Removal of the thyroid lobe affected by clinically detectable disease and the isthmus (hemithyroidectomy)
Prophylactic lymphadenectomy	Lymphadenectomy	Selective neck dissection of only the clinically involved node levels
RAI scintigraphic scan to seek any subclinical metastases	Staging	No RAI scintigraphic scan (macrostaging instead of microstaging)
Treatment with 131I ablation, where necessary	Post-operative treatment	Lifelong TSH suppression therapy to control subclinical disease
Serum thyroglobulin level is a very sensitive marker of post-treatment relapse	Follow-up	Presence of thyroid tissue could prevent the effective use of thyroglobulin assay as a marker of tumor relapse, even if a higher cut-off than 0 could be used
Hypoparathyroidism (36%) Recurrent laryngeal nerve paralysis and spinal accessory nerve paralysis (28%) Risk of iatrogenic effects of metabolic radiotherapy	Risk of permanent morbidity	Very low, if ever

studies are currently available that would provide definite evidence in favor of one or the other strategy. Both strategies are discussed in detail and summarized in Table 16.3.

16.2.5.1 Surgery

The development of a standard treatment strategy for the treatment of childhood thyroid cancer suffers from the same affliction that affects other rare pediatric tumors: the reliance on retrospective studies and the absence of prospective clinical trials (Spinelli et al. 2004; Dinauer et al. 2008; Collini et al. 2007). Though the optimal primary surgical intervention is still unclear, future prospective trials comparing various procedures should be the goal. One very important factor for successful treatment of childhood thyroid cancer is the availability to receive treatment at a facility with the appropriate specialists with a large experience in the treatment of thyroid cancer. A multidisciplinary effort, that may include surgeons, pediatric oncologists, medical oncologists, and nuclear medicine physicians, would be ideal.

The vast majority of patients undergo total thyroidectomy with or without lymph node dissection. Advantages of this radical approach are:

- Upgrading progression-free survival (PFS) and overall survival (OS).
- Ablative radioiodine therapy can be performed.
- Metastases can be sensitively detected by whole-body scintigraphy.
- Use of thyroglobulin as sensitive marker of post-treatment relapse.
- Numerous children with PTC have multifocal disease, so all thyroid tissue potentially at risk of containing multiple neoplastic foci is removed (Welch Dinauer et al. 1998; Miccoli et al. 1998; De Jong et al. 1992).

Some authors recommend total thyroidectomy even in microcarcinoma (Ogilvie et al. 2010). For selected cases, a more conservative approach is discussed (Massimino et al. 2006). A more conservative treatment approach has not been universally applied. This approach has been developed at several institutions and should be done as part of an organized clinical

trial. Only selected patients with tumor limited to one lobe with or without clinical evidence of monolateral nodal metastases are eligible. The main argument for the conservative approach is the excellent prognosis of DTC in children and adolescents despite a more advanced stage at presentation and a more aggressive clinical course (Danese et al. 1997; Chow et al. 2004). Presence of lymph node or distant metastases does not influence mortality in children. The chance of dedifferentiation of microscopic disease over the years is only theoretical. More aggressive procedures, especially if applied in children under 16 years of age, are closely related to a morbidity increase (permanent hypoparathyroidism and recurrent nerve palsy) (La Quaglia et al. 1988; van Santen et al. 2004). Minimal approach is hemithyroidectomy consisting of lobectomy plus isthmectomy. If further surgery is required, no resection in an already operated bed associated with higher complications must be performed (Shaha 2008; Levin et al. 1992).

So as long as there are no prospective trials investigating different therapeutical regimes, the debate will continue. If a conservative approach is to be followed, the role of a pathologist, experienced in thyroid pathology and in particular in the diagnosis of pediatric thyroid carcinomas, becomes critical in the application of the conservative approach.

16.2.5.2 Radioiodine Therapy and Hormonal Manipulation

The radioactive isotope 131I can be administered for selective irradiation of remnant thyroid tissue, microscopic foci of carcinoma, and distant metastases if a radical surgical approach has been used. Radioiodine uptake in carcinoma cells depends on the expression of the sodium–iodide symporter (NIS). In pediatric DTC, the NIS is expressed stronger when compared with adult tumors (Jarzab et al. 2005). That may be one of the reasons why DTC in children are more sensitive to hormonal manipulation and have a better prognosis despite more advanced disease at diagnosis.

The first ablative radioiodine therapy (RIT) after total thyroidectomy is an adjuvant modality to eliminate regularly remaining thyroid tissue and increase sensitivity of thyroglobulin assay and whole-body scintigraphy in follow-up. RIT requires adequate TSH stimulation. It can be achieved endogenously via L-thyroxin withdrawal within 14 days in children (Kuijt and Huang 2005). The use of recombinant thyrotropin (rhTSH) in children is safe; well-tolerated and adequate TSH levels can be achieved (Luster et al. 2009; Ralli et al. 2005).

Functioning of the thyroid is dependent on TSH, whose synthesis and release depend on thyroid-releasing hormone (TRH), produced in the hypothalamus and secreted into the pituitary (Crile 1966; Gharib et al. 1987). Suppression of TSH secretion (TSH < 0.1 mU/l) has the aim to prevent growth of hidden microfoci, residual tumor, or metastases, respectively.

Used activities vary from 50 MBq/kg for ablation to 100 (–150) MBq/kg for metastatic disease (Franzius et al. 2007). Monitoring of the pulmonary function is recommended to detect radiation-induced pulmonary fibrosis, which is a rare sequela of RIT.

16.2.6 Follow-up

Whole-body scintigraphy is repeated after 6–12 months from the metabolic treatment, and the RIT can be repeated in case of persistent disease. The goal of this strategy is to obtain a negative scan and a thyroglobulin with an undeterminable value. Thyroglobulin concentration after ablative RIT is a strong predictor of disease recurrence (Pelttari et al. 2010). Low-risk patients with undetectable basal thyroglobulin should receive at least one rhTSH-stimulated thyroglobulin because of the low predictive value for recurrence of basal thyroglobulin (Diaz-Soto et al. 2011).

16.2.7 Postoperative Complications and Their Treatment

Subsequently to radical surgery, high percentages of permanent postoperative complications are documented. After total thyroidectomy, permanent hypoparathyroidism and recurrent laryngeal nerve paralysis often occur, while after neck dissection, spinal accessory nerve paralysis is the major complication. In addition, iatrogenic effects of RAI therapy are reported. Postoperative complications are high in almost all pediatric series, especially after total thyroidectomy, also if performed by pediatric surgeons or by neck surgeons devoted to thyroid surgery. Hypoparathyroidism accounts for 0–36% (Bargren et al. 2009; Machens and Dralle 2009; Massimino et al. 2006; Reeve and Thompson 2000) and recurrent nerve palsy from 0% to 28% (Crile 1966;

Table 16.4 Manifestations in MEN 2 syndrome and their frequencies

	MEN 2A (%)	MEN 2B (%)
MTC (Brandi et al. 2001; Iihara et al. 1997)	90–100	100
Pheochromocytoma (Brandi et al. 2001; Modigliani et al. 1998)	50	50
Hyperparathyroidism (Brandi et al. 2001; Modigliani et al. 1998)	20–30	–
Intestinal ganglioneuromatosis	–	40–100
Marfanoid habitus	–	>95
Stigmata	–	>95

Verburg et al. 2009). Age below 16 years is at risk of being accompanied by major complications. In children, recurrent nerves are at major risk of being injured, and parathyroid glands are very small, often hidden into the thyroid parenchyma, difficult to recognize and with a light vascularization. These complications can be very severe in developing age. To make a pragmatic example, also, their support can be difficult and expensive. An adolescent girl around the age of menarche, when deprived of parathyroid normal function, needs frequent electrolyte assays, more than biweekly, to have a valid calcium, vitamin D, and/or parathormone support. Any calcium/phosphorus balance alteration can reflect in alteration of the body mass and in possible later consequences on the harmonic body growth. All these issues suggest that the management of children with thyroid carcinoma should be performed in selected centers.

16.2.8 Prognosis

Children and adolescents with DTC have an excellent prognosis despite the more aggressive behavior when compared with adults (Jarzab and Handkiewicz-Junak 2007). Nevertheless, fatal outcome occurs in some cases. It is a well-known phenomenon that the outcome of pediatric PTC is independent of strong prognostic factors of adults, such as low- versus high-risk histological subtype, extrathyroid local invasion into soft tissue of the neck, presence of distant metastases, site of distant metastatic spread, occurrence of relapse, and type of surgery (Verburg et al. 2009; Collini et al. 2006b).

16.3 Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arising from the parafollicular C cells is associated with inherited tumor syndromes. The multiple endocrine neoplasias (MEN) type 2A, 2B, and also familial medullary thyroid carcinoma (FMTC) are characterized by bilateral multifocal MTC invariably in a background of C-cell hyperplasia, the inherited predisposing abnormality. In MEN 2A, besides the calcitonin-producing thyroid tumor, pheochromocytoma and parathyroid adenoma/hyperplasia causing hyperparathyroidism are found. MTC, pheochromocytoma, and typical stigmatas characterize patients suffering from MEN 2B (Table 16.4). The FMTC is diagnosed if at least four cases occur in a family in the absence of other MEN 2 manifestations.

MTC usually is the first tumor to develop in patients with MEN 2 and is the most common cause of death among these patients (Szinnai et al. 2007). The malignancy is particularly aggressive in patients with MEN 2B and may occur even in infancy (Yin et al. 2006). Different germline point mutations of the REarranged during Transfection (RET) proto-oncogene are involved in the pathogenesis of MTC and MEN 2, respectively, with consequences on management of affected children (Raue and Frank-Raue 2009; Machens and Dralle 2007). Screening for MEN 2 of affected kindreds reveals children with MEN 2, who should undergo prophylactic thyroidectomy before developing MTC (Table 16.5). A strong genotype–phenotype correlation is known, leading to the discrimination in highest-, high-, and least-high-risk mutations, respectively (Table 16.5). MEN 2A is frequently caused by mutation in codon 634 and MEN 2B by mutation in codon 918.

More than 90% of patients with MEN 2B harbor de novo mutations in the RET proto-oncogene. These index cases without any family history are at high risk for developing advanced MTC with high mortality. The distinct physical appearance of children with MEN 2B, e.g., mucosal neuromas of the tongue, lips, inner eyelids, marfanoid body habitus, are not appreciated before the occurrence of the thyroid tumor.

Table 16.5 Timing of prophylactic thyroidectomy in MEN 2 (Machens and Dralle 2007; Brandi et al. 2001; Frank-Raue et al. 2006)

RET mutation	Time of surgery	Operation
Least-high-risk level (609, 768, 790, 791, 804, 891)	<5–10 years or pPT	Total thyroidectomy
High-risk level (611, 618, 620, 630, **634**)	<5 years	Total thyroidectomy
Highest-risk level (883, **918**)	<1/2–1 years	Total thyroidectomy with central lymph node dissection

Premonitory symptoms preceding metastatic MTC are constipation since infancy and inability to cry tears (Brauckhoff et al. 2004). Children with sporadic MTC commonly present with palpable thyroid nodule.

In MEN 2A, no accompanying visible signs are found. An association with Hirschsprung disease or cutaneous lichen amyloidosis is described (Cohen et al. 2002; Verga et al. 2003).

Calcitonin levels represent an accurate and sensitive marker for both preoperative diagnosis and follow-up of MTC (Cohen et al. 2000; Melvin et al. 1971). Pentagastrin testing may be helpful in differentiating C-cell hyperplasia from MTC in cases of moderately elevated basal calcitonin (Milone et al. 2010).

The most important therapeutical option is the radical approach, with the surgical resection of all tumor localizations, since no curative medical therapy is available (Kloos et al. 2009). In recent years, targeted therapy with small molecules such as tyrosine kinase inhibitors and RET kinase inhibitors have been studied in clinical trials with partial responses in up to 30% (Lanzi et al. 2009; Puxeddu et al. 2011; Sherman 2010). The most important prognostic factor is clinical stage at diagnosis. Patients with lymph node or distant metastases are at risk of relapse or fatal outcome (Bergholm et al. 1997).

16.3.1 Pediatric Thyroid Cancer: A Model for Collaboration

The treatment of pediatric thyroid cancer is complex and should be managed by a medical team with appropriate experience and skills. The treatment of thyroid cancer in adult patients has been informed by several studies, and general guidelines exist. Pediatric oncologists have tried to extrapolate from these guidelines, but sufficient data do not exist. One aspect of the treatment debate is the fear of exposing children to potential late toxicity. It is known that pediatric thyroid cancer may be more aggressive than thyroid cancer in adults. However, pediatric patients respond well to hormonal manipulation with TSH suppression, and the mortality from pediatric thyroid cancer is very low. In the US, the Children's Oncology Group realizes that, for many "rare" cancers, clinical trials are unlikely. For these tumors, clinical guidelines are being developed. The same strategy is being pursued in other countries. It is important to emphasize that as one develops guidelines, one must try to validate them with careful attention to outcomes. For this reason, the Italian approach to a more conservative approach serves as an excellent example (Table 16.3). Guidelines were established, and data are being collected that might inform future international collaborative trials.

References

Aghini-Lombardi F, Antonangeli L, Martino E et al (1999) The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. J Clin Endocrinol Metab 84(2):561–566

Bargren AE, Meyer-Rochow GY, Delbridge LW, Sidhu SB, Chen H (2009) Outcomes of surgically managed pediatric thyroid cancer. J Surg Res 156(1):70–73

Bell B, Mazzaferri EL (1993) Familial adenomatous polyposis (Gardner's syndrome) and thyroid carcinoma. A case report and review of the literature. Dig Dis Sci 38(1):185–190

Bergholm U, Bergstrom R, Ekbom A (1997) Long-term follow-up of patients with medullary carcinoma of the thyroid. Cancer 79(1):132–138

Bhatia S, Yasui Y, Robison LL et al (2003) High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 21(23):4386–4394

Brandi ML, Gagel RF, Angeli A et al (2001) Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 86(12):5658–5671

Brauckhoff M, Gimm O, Weiss CL et al (2004) Multiple endocrine neoplasia 2B syndrome due to codon 918 mutation: clinical manifestation and course in early and late onset disease. World J Surg 28(12):1305–1311

Buckwalter JA, Gurll NJ, Thomas CG Jr (1981) Cancer of the thyroid in youth. World J Surg 5(1):15–25

Chaukar DA, Rangarajan V, Nair N et al (2005) Pediatric thyroid cancer. J Surg Oncol 92(2):130–133

Chen WK, Lee CH, Wang HC, Lui WY, Wei CF (1994) Thyroid cancer in children and adolescents. Zhonghua Yi Xue Za Zhi (Taipei) 54(6):400–406

Chow SM, Law SC, Mendenhall WM et al (2004) Differentiated thyroid carcinoma in childhood and adolescence-clinical course and role of radioiodine. Pediatr Blood Cancer 42(2):176–183

Cohen R, Campos JM, Salaun C et al (2000) Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). J Clin Endocrinol Metab 85(2):919–922

Cohen MS, Phay JE, Albinson C et al (2002) Gastrointestinal manifestations of multiple endocrine neoplasia type 2. Ann Surg 235(5):648–654

Collini P, Sampietro G, Pilotti S (2004) Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hurthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. Histopathology 44(1):35–39

Collini P, Massimino M, Leite SF et al (2006a) Papillary thyroid carcinoma of childhood and adolescence: a 30-year experience at the Istituto Nazionale Tumori in Milan. Pediatr Blood Cancer 46(3):300–306

Collini P, Mattavelli F, Pellegrinelli A, Barisella M, Ferrari A, Massimino M (2006b) Papillary carcinoma of the thyroid gland of childhood and adolescence: morphologic subtypes, biologic behavior and prognosis: a clinicopathologic study of 42 sporadic cases treated at a single institution during a 30-year period. Am J Surg Pathol 30(11):1420–1426

Collini P, Mattavelli F, Spinelli C, Massimino M (2007) Treatment of sporadic nonmedullary thyroid carcinomas in pediatric age. Expert Rev Anticancer Ther 7(1):23–30

Crile G Jr (1966) Endocrine dependency of papillary carcinoma of the thyroid. JAMA 195(9):721–724

Danese D, Gardini A, Farsetti A, Sciacchitano S, Andreoli M, Pontecorvi A (1997) Thyroid carcinoma in children and adolescents. Eur J Pediatr 156(3):190–194

De Jong SA, Demeter JG, Lawrence AM, Paloyan E (1992) Necessity and safety of completion thyroidectomy for differentiated thyroid carcinoma. Surgery 112(4):734–737

De Keyser LF, Van Herle AJ (1985) Differentiated thyroid cancer in children. Head Neck Surg 8(2):100–114

DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds) (2004a) Pathology and genetics. Tumours of endocrine organs. In: World Health Organization Classification of Tumours. IARC, Lyon

DeLellis RA, Lloyd RV, Heitz PU, Eng C (2004b) World Health Organization Classification of Tumours. Pathology and genetics of tumours of endocrine organs. IARC, Lyon

Díaz-Soto G, Puig-Domingo M, Martínez-Pino I, Martínez de Osaba MJ, Mora M, Rivera-Fillat F, Halperin I (2011) Do thyroid cancer patients with basal undetectable Tg measured by current immunoassays require rhTSH testing? Exp Clin Endocrinol Diabetes 119:348–352.

Dinauer CA, Breuer C, Rivkees SA (2008) Differentiated thyroid cancer in children: diagnosis and management. Curr Opin Oncol 20(1):59–65

dos Santos Silva I, Swerdlow AJ (1993) Sex differences in the risks of hormone-dependent cancers. Am J Epidemiol 138(1):10–28

Farahati J, Bucsky P, Parlowsky T, Mader U, Reiners C (1997) Characteristics of differentiated thyroid carcinoma in children and adolescents with respect to age, gender, and histology. Cancer 80(11):2156–2162

Farahati J, Parlowsky T, Mader U, Reiners C, Bucsky P (1998) Differentiated thyroid cancer in children and adolescents. Langenbecks Arch Surg 383(3–4):235–239

Farahati J, Reiners C, Demidchik EP (1999) Is the UICC/AJCC classification of primary tumor in childhood thyroid carcinoma valid? J Nucl Med 40(12):2125

Frank-Raue K, Buhr H, Dralle H et al (2006) Long-term outcome in 46 gene carriers of hereditary medullary thyroid carcinoma after prophylactic thyroidectomy: impact of individual RET genotype. Eur J Endocrinol 155(2): 229–236

Franzius C, Dietlein M, Biermann M et al (2007) Procedure guideline for radioiodine therapy and 131iodine whole-body scintigraphy in paediatric patients with differentiated thyroid cancer. Nuklearmedizin 46(5):224–231

Gharib H, Goellner JR (1993) Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 118(4):282–289

Gharib H, James EM, Charboneau JW, Naessens JM, Offord KP, Gorman CA (1987) Suppressive therapy with levothyroxine for solitary thyroid nodules. A double-blind controlled clinical study. N Engl J Med 317(2):70–75

Hegedus L, Karstrup S (1998) Ultrasonography in the evaluation of cold thyroid nodules. Eur J Endocrinol 138(1):30–31

Herle AJ, Uller RP (1975) Elevated serum thyroglobulin. A marker of metastases in differentiated thyroid carcinomas. J Clin Invest 56(2):272–277

Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE (2009) Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res 156(1):167–172

Iihara M, Yamashita T, Okamoto T et al (1997) A nationwide clinical survey of patients with multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma in Japan. Jpn J Clin Oncol 27(3):128–134

Jarzab B, Handkiewicz-Junak D (2007) Differentiated thyroid cancer in children and adults: same or distinct disease? Hormones (Athens) 6(3):200–209

Jarzab B, Handkiewicz-Junak D, Wloch J (2005) Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. Endocr Relat Cancer 12(4):773–803

Kazakov VS, Demidchik EP, Astakhova LN (1992) Thyroid cancer after Chernobyl. Nature 359(6390):21

Kloos RT, Eng C, Evans DB et al (2009) Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 19(6):565–612

Kuijt WJ, Huang SA (2005) Children with differentiated thyroid cancer achieve adequate hyperthyrotropinemia within 14 days of levothyroxine withdrawal. J Clin Endocrinol Metab 90(11):6123–6125

La Quaglia MP, Corbally MT, Heller G, Exelby PR, Brennan MF (1988) Recurrence and morbidity in differentiated thyroid carcinoma in children. Surgery 104(6):1149–1156

Lanzi C, Cassinelli G, Nicolini V, Zunino F (2009) Targeting RET for thyroid cancer therapy. Biochem Pharmacol 77(3): 297–309

Lassaletta AL, Melchor Diaz MA, Gavilanes PJ, Martin HG, de Vergas GJ (1997) Thyroid nodules: factors suggestive of malignancy. Acta Otorrinolaringol Esp 48(3):220–224

Levin KE, Clark AH, Duh QY, Demeure M, Siperstein AE, Clark OH (1992) Reoperative thyroid surgery. Surgery 111(6):604–609

Liesenkotter KP, Kiebler A, Stach B, Willgerodt H, Gruters A (1997) Small thyroid volumes and normal iodine excretion in Berlin schoolchildren indicate full normalization of iodine supply. Exp Clin Endocrinol Diabetes 105(Suppl 4):46–50

Lugo-Vicente H, Ortiz VN (1998) Pediatric thyroid nodules: insights in management. Bol Asoc Med P R 90(4–6):74–78

Luster M, Handkiewicz-Junak D, Grossi A et al (2009) Recombinant thyrotropin use in children and adolescents with differentiated thyroid cancer: a multicenter retrospective study. J Clin Endocrinol Metab 94(10):3948–3953

Machens A, Dralle H (2007) Genotype-phenotype based surgical concept of hereditary medullary thyroid carcinoma. World J Surg 31(5):957–968

Machens A, Dralle H (2009) Age disparities in referrals to specialist surgical care for papillary thyroid cancer. Eur J Surg Oncol 35(12):1312–1317

Massimino M, Collini P, Leite SF et al (2006) Conservative surgical approach for thyroid and lymph-node involvement in papillary thyroid carcinoma of childhood and adolescence. Pediatr Blood Cancer 46(3):307–313

Melvin KE, Miller HH, Tashjian AH Jr (1971) Early diagnosis of medullary carcinoma of the thyroid gland by means of calcitonin assay. N Engl J Med 285(20):1115–1120

Mettler FA Jr, Williamson MR, Royal HD et al (1992) Thyroid nodules in the population living around Chernobyl. JAMA 268(5):616–619

Miccoli P, Antonelli A, Spinelli C, Ferdeghini M, Fallahi P, Baschieri L (1998) Completion total thyroidectomy in children with thyroid cancer secondary to the Chernobyl accident. Arch Surg 133(1):89–93

Miccoli P, Minuto MN, Ugolini C et al (2008) Papillary thyroid cancer: pathological parameters as prognostic factors in different classes of age. Otolaryngol Head Neck Surg 138(2):200–203

Milone F, Ramundo V, Chiofalo MG et al (2010) Predictive value of pentagastrin test for preoperative differential diagnosis between C-cell hyperplasia and medullary thyroid carcinoma in patients with moderately elevated basal calcitonin levels. Clin Endocrinol (Oxf) 73(1):85–88

Modigliani E, Cohen R, Campos JM et al (1998) Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'etude des tumeurs a calcitonine. Clin Endocrinol (Oxf) 48(3):265–273

Newman KD, Black T, Heller G et al (1998) Differentiated thyroid cancer: determinants of disease progression in patients <21 years of age at diagnosis: a report from the Surgical Discipline Committee of the Children's Cancer Group. Ann Surg 227(4):533–541

Ng Tang Fui SC, Hoffenberg R, Maisey MN, Black EG (1979) Serum thyroglobulin concentrations and whole-body radioiodine scan in follow-up of differentiated thyroid cancer after thyroid ablation. Br Med J 2(6185):298–300

Niedziela M (2006) Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer 13(2):427–453

Ogilvie JB, Patel KN, Heller KS (2010) Impact of the 2009 American Thyroid Association guidelines on the choice of operation for well-differentiated thyroid microcarcinomas. Surgery 148(6):1222–1226

Okayasu I, Fujiwara M, Hara Y, Tanaka Y, Rose NR (1995) Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and white and African Americans. Cancer 76(11):2312–2318

Ott RA, Calandra DB, McCall A, Shah KH, Lawrence AM, Paloyan E (1985) The incidence of thyroid carcinoma in patients with Hashimoto's thyroiditis and solitary cold nodules. Surgery 98(6):1202–1206

Parisi MT, Mankoff D (2007) Differentiated pediatric thyroid cancer: correlates with adult disease, controversies in treatment. Semin Nucl Med 37(5):340–356

Pelttari H, Valimaki MJ, Loyttyniemi E, Schalin-Jantti C (2010) Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. Eur J Endocrinol 163(5): 757–763

Puxeddu E, Romagnoli S, Dottorini ME (2011) Targeted therapies for advanced thyroid cancer. Curr Opin Oncol 23:13–21.

Ralli M, Cohan P, Lee K (2005) Successful use of recombinant human thyrotropin in the therapy of pediatric well-differentiated thyroid cancer. J Endocrinol Invest 28(3):270–273

Raue F, Frank-Raue K (2009) Genotype-phenotype relationship in multiple endocrine neoplasia type 2. Implications for clinical management. Hormones (Athens) 8(1):23–28

Reeve T, Thompson NW (2000) Complications of thyroid surgery: how to avoid them, how to manage them, and observations on their possible effect on the whole patient. World J Surg 24(8):971–975

Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice JD Jr (1989) Thyroid neoplasia following low-dose radiation in childhood. Radiat Res 120(3):516–531

Rosai J, Carcangiu ML, DeLellis RA (2011) Tumors of the thyroid gland. In: Rosai J, Sobin H (eds) Atlas of tumor pathology. Armed Forces Institute of Pathology, Washington DC

Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA (1988) Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. J Clin Endocrinol Metab 67(3):501–508

Schlumberger M, de Vathaire F, Travagli JP et al (1987) Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. J Clin Endocrinol Metab 65(6): 1088–1094

Shaha AR (2008) Revision thyroid surgery - technical considerations. Otolaryngol Clin North Am 41(6):1169–1183, x

Sherman SI (2010) Targeted therapy of thyroid cancer. Biochem Pharmacol 80(5):592–601

Showalter TN, Siegel BA, Moley JF, Baranski TJ, Grigsby PW (2008) Prognostic factors in patients with well-differentiated thyroid cancer presenting with pulmonary metastasis. Cancer Biother Radiopharm 23(5):655–659

Spinelli C, Bertocchini A, Antonelli A, Miccoli P (2004) Surgical therapy of the thyroid papillary carcinoma in children: experience with 56 patients < or =16 years old. J Pediatr Surg 39(10):1500–1505

Stevens C, Lee JK, Sadatsafavi M, Blair GK (2009) Pediatric thyroid fine-needle aspiration cytology: a meta-analysis. J Pediatr Surg 44(11):2184–2191

Szinnai G, Sarnacki S, Polak M (2007) Hereditary medullary thyroid carcinoma: how molecular genetics made multiple endocrine neoplasia type 2 a paediatric disease. Endocr Dev 10:173–187

van Santen HM, Aronson DC, Vulsma T et al (2004) Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience. Eur J Cancer 40(11):1743–1751

Verburg FA, Mäder U, Luster M, Reiners C (2009) Histology does not influence prognosis in differentiated thyroid carcinoma when accounting for age, tumour diameter, invasive growth and metastases. Eur J Endocrinol 160:619–624

Verga U, Fugazzola L, Cambiaghi S et al (2003) Frequent association between MEN 2A and cutaneous lichen amyloidosis. Clin Endocrinol (Oxf) 59(2):156–161

Welch Dinauer CA, Tuttle RM, Robie DK et al (1998) Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. Clin Endocrinol (Oxf) 49(5):619–628

Wiersinga WM (2001) Thyroid cancer in children and adolescents–consequences in later life. J Pediatr Endocrinol Metab 14(Suppl 5):1289–1296

Yin M, King SK, Hutson JM, Chow CW (2006) Multiple endocrine neoplasia type 2B diagnosed on suction rectal biopsy in infancy: a report of 2 cases. Pediatr Dev Pathol 9(1):56–60

Yip FW, Reeve TS, Poole AG, Delbridge L (1994) Thyroid nodules in childhood and adolescence. Aust N Z J Surg 64(10):676–678

Zimmerman D, Hay ID, Gough IR et al (1988) Papillary thyroid carcinoma in children and adults: long-term follow-up of 1039 patients conservatively treated at one institution during three decades. Surgery 104(6):1157–1166

Nasopharyngeal Carcinoma

17

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Contents

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17.1 Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignant tumor in childhood not only in Europe but also in Asia, where the highest incidence of NPC in adult patients is seen. NPC represents one of the most frequent epithelial tumors of the child in intermediate risk regions. However, distinguishing malignant tumors from the more common and numerous benign causes of neck masses in childhood is crucial, as many malignant conditions have an excellent prognosis with appropriate oncological management. The worldwide incidence of NPC in children and adolescents between 0 and 14 years is 0.1 per 100,000 and follows a bimodal age distribution with a first peak between 10 and 20 years and a second peak between that fourth and sixth decades (Bray et al. 2008; Wei and St Sham 2005). Males are more frequently affected than females, with

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a male to female ratio of 2:1. In the United States, the incidence is higher in African-American children than in children of other races, but this racial predilection is lost in older ages. While 10–15% of cases occur in patients younger than 30 years of age, it makes up only 1% of childhood malignancies. NPC has a distinct epidemiology, etiology, and clinical course compared with other head and neck squamous cell carcinomas, and its pathogenesis is multifactorial. Genetic predisposition and epigenetic alterations particularly related to Epstein–Barr virus (EBV) infection play a major role in the initiation and progression of NPC (Sultan et al. 2010; Cheuk et al. 2011; Dittmer et al. 2008; Wong et al. 2004).

17.2 Symptoms

Young patients with nasopharyngeal carcinoma frequently present with symptoms resulting from mass effect. Nasal symptoms, such as epistaxis and nasal obstruction, are almost always present and are secondary to the presence of the tumor in the nasopharynx. Secondly, otologic symptoms, such as hearing loss and tinnitus, which are related to the dysfunction of the Eustachian tube caused by the lateroposterior extension of the tumor into the paranasopharyngeal space. Thirdly, cranial nerve palsies, commonly the fifth and sixth cranial nerves, resulting from the extension of the tumor superiorly, leading to skull base erosion; the patient might experience headache, diplopia, facial pain, and numbness. A retrospective analysis of 4,768 patients identified the symptoms at presentation as neck mass (75.8%), nasal (73.4%), aural (62.4%), headache (34.8%), diplopia (10.7%), facial numbness (7.6%), weight loss (6.9%), and trismus (3.0%). The physical signs present at diagnosis were enlarged neck node (74.5%) and cranial nerve palsy (20.0%) (Ozyar et al. 1994; Lee et al. 1997). Since the nasal and auditory symptoms are nonspecific and a thorough examination of the nasopharynx is not easy, the majority of NPC patients are only diagnosed when the tumor has reached an advanced stage. Therefore, young patients had significantly more advanced-stage disease compared with the group of adult patients. Mostly neck masses are observed, usually appearing first in the upper neck. NPC is characterized by a very important locoregional extension as well as a high rate of distant metastases (Mertens et al. 1997; Tang et al. 2010).

17.3 Pathogenesis

NPC presents as a complex disease caused by an interaction of the oncogenic gammaherpesvirus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process.

A monoclonal EBV infection is found in more than 98% of preinvasive lesions. The EBV-infected epithelial cells express the EBV-antigens EBNA1, LMP 1, and 2 as well as the EBERs. In vitro and in vivo models have shown that LMP1 and, in particular, LMP2 play a role in the malignant transformation of the NPC cells (Raab-Traub 2002).

While nasopharyngeal carcinoma is a rare malignancy in most parts of the world, it is one of the most common cancers in Southeast Asia. Epidemiologic studies conducted in that region have provided an invaluable insight into our current understanding of NPC pathogenesis. The pathogenesis of NPC is influenced by three major factors: environmental factors, such as certain herbs and salted fish consumed in regions with an elevated incidence of NPC; genetic factors, as documented by familial cases that suggest a genetically determined susceptibility; and infectious factors, as documented by the evidence of early EBV infection (Ren et al. 2010).

17.3.1 Environmental Factors

A large number of case-control studies conducted in diverse populations in Southeast Asia, Alaska, the Mediterranean basin, and North America have shown that consumption of salted fish and other preserved foods containing large amounts of nitrosodimethylamine may predispose to the development of NPC (Chang and Adami 2006).

17.3.2 Genetic Factors

Studies in Southeast China demonstrated an increased risk of NPC for individuals with HLA-A2. A recent study detected a consistent association between NPC

and the prevalent Chinese HLA-A2 subtype (HLA-A*0207) but not the prevalent Caucasian subtype (HLA-A*0201) (Hildesheim et al. 2002). The HLA types of AW19, BW46, and B17 have also been reported to be associated with an increased risk, whereas HLA-A11 is associated with a decreased risk (Liebowitz 1994). Significant complex multiple chromosome aberrations are often demonstrated.

17.3.3 Epstein–Barr Virus

EBV is consistently detected in NPC patients from regions of high and low incidence. Using EBV-encoded RNA (EBER) in situ hybridization, EBER signal was present in virtually all tumor cells. Premalignant lesions of the nasopharyngeal epithelium have also been shown to harbor EBV, and the EBV DNA is clonal, suggesting that EBV infection occurs in the early phases of carcinogenesis (Gulley 2001). In the past, NPC was called lymphoepithelioma, as the malignant epithelial cells of the nasopharynx frequently intermingled with lymphoid cells in the nasopharynx (Godtfredsen 1944). The histological classification of nasopharyngeal carcinoma proposed by the World Health Organization (WHO) in 1978 categorized tumors into three types. Type I were the typical keratinizing squamous cell carcinomas similar to those found in the rest of the upper aerodigestive tract. Type II included nonkeratinizing squamous carcinomas and type III carcinomas were the undifferentiated carcinomas (Micheau et al. 1978; Shanmugaratnam 1980; Marks et al. 1998).

Table 17.1 shows the WHO classification modified by Krüger and Wustrow indicating the varying degrees of lymphoid infiltration, whereby the undifferentiated NPC with lymphoid infiltration corresponds to the entities described in 1921 as lymphoepithelioma by Schmincke and nonkeratinizing epithelium carcinoma by Regaud. Histological variants are strictly associated with increased titers against EBV antigen (Krueger and Wustrow 1981).

Table 17.1 WHO classification modified by Krüger and Wustrow

Squamous cell carcinoma (keratinizing)	Type I
Squamous cell carcinoma (nonkeratinizing)	
– Without lymphoid infiltration	Type IIa
– With lymphoid infiltration	Type IIb
Undifferentiated (anaplastic carcinoma)	
– Without lymphoid infiltration	Type IIIa
– With lymphoid infiltration	Type IIIb

17.4 Staging Systems

There are various ways of staging nasopharyngeal carcinomas. At present, the American Joint Committee on Cancer Staging and End Result Reporting/International Union Against Cancer (the 6th edition of the *AJCC staging*) system is preferred in Europe and America. This staging system follows the classical TNM criteria. The Ho's system is frequently used in Asia (Lee et al. 1999).

17.4.1 Primary Tumor (T)

T1 Tumor confined to the nasopharynx
T2 Tumor extends to soft tissues of oropharynx and/or nasal fossa
T2a Without parapharyngeal extension
T2b With parapharyngeal extension
T3 Tumor invades bony structures and/or paranasal sinuses
T4 Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, orbit, and direct invasion of first or second cervical vertebra, hypopharynx, orbit, or masticator space

17.4.2 Regional Lymph Nodes (N)

N0 No regional lymph node metastasis
N1 Unilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N2 Bilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N3 Metastasis in lymph node(s)
N3a >6 cm in greatest dimension
N3b Extension to the supraclavicular fossa

17.4.3 Distant Metastasis (M)

M0 No distant metastasis
M1 Presence of distant metastasis

Table 17.2 Stage-related definition of risk groups

Stage grouping	
Stage I	T1 N0 M0
Stage IIA	T2a N0 M0
Stage IIB	T1-2 N1 M0
	T2b N0-1 M0
Stage III	T1-2 N2 M0
	T3 N0-2 M0
Stage IVA	T4 N0-2 M0
Stage IVB	Any T N3 M0
Stage IVC	Any T Any N M1

17.4.4 Definition of Risk Groups

Staging directly correlates with outcome, and in general, two large groups of patients are identified based on rates of local control and risk of metastatic disease. Patients with stages I–IIA have an excellent outcome, with survival rates in excess of 75–80%, whereas patients with stages IIB–IV have lower survival (Lee et al. 1992; Wee et al. 2005; Ali and al-Sarraf 2000; Al-Sarraf et al. 1998) (Table 17.2) (Figs. 17.1 and 17.2).

17.5 Diagnosis

Clinical examination, including endoscopic examination of the nasopharynx, can provide very valuable information on mucosal involvement and local tumor extension. A definitive histological diagnosis should require a positive biopsy taken from the tumor in the nasopharynx, although a nodal biopsy in the appropriate context may also be diagnostic. Clinical examination cannot, however, determine a deep extension of the tumor, such as skull base erosion and intracranial spread.

Cross-sectional imaging has revolutionized the management of NPC. In terms of contribution to staging, MRI can identify the paranasopharyngeal extension as one of the most common modes of extension of NPC and perineural spread through the foramen ovale as an important route of intracranial extension (Sham et al. 1991). Perineural spread through the foramen ovale also accounts for the CT evidence of cavernous sinus involvement without skull base erosion (Chong et al. 1996). Positron emission tomography (PET) may provide an additional tool for the initial diagnosis and staging and help in the evaluation of disease response after therapy (King et al. 2008).

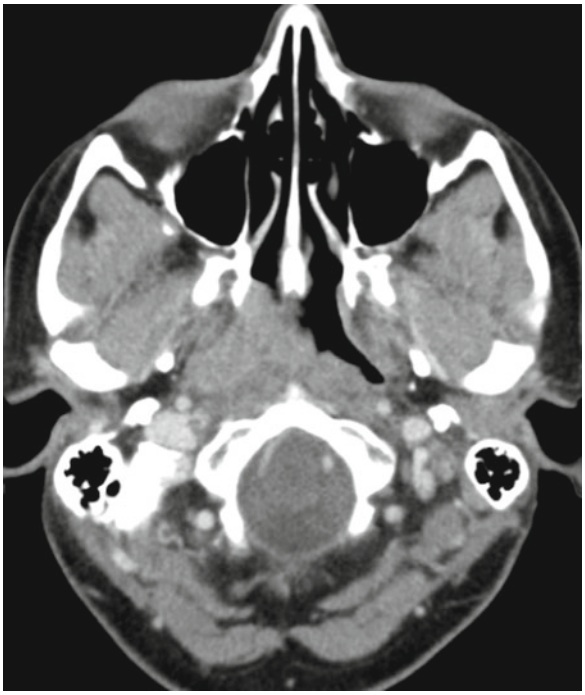

Fig. 17.1 Axial MRI shows the typical primary tumor of NPC (T3) extending into the right infratemporal fossa

17.5.1 Epstein–Barr Virus

Epstein–Barr virus (EBV) or human herpes virus 4 (HHV4) is an oncogenic c-herpes virus associated with malignancies that develop in NPC. EBV is consistently detected in patients with nasopharyngeal carcinoma, and its ability to establish latent infection of their host cells and to induce proliferation of the latently infected cells is directly involved in NPC pathogenesis (Niedobitek and Young 1994). Under normal circumstances, EBV infection is restricted to humans, although some types of monkeys can be infected experimentally (Bornkamm 1984).

EBV-encoded RNA signal has been shown to be present in nearly all tumor cells, whereas EBV RNA is absent from the adjacent normal tissue, except perhaps for a few scattered lymphoid cells. Premalignant lesions of the nasopharyngeal epithelium have also been shown to harbor EBV RNA, which suggests that the infection occurs in the early phases of carcinogenesis. Detection of a single form of viral DNA suggests that the tumors are clonal proliferations of a single cell that was initially infected with EBV (Lo et al. 2000).

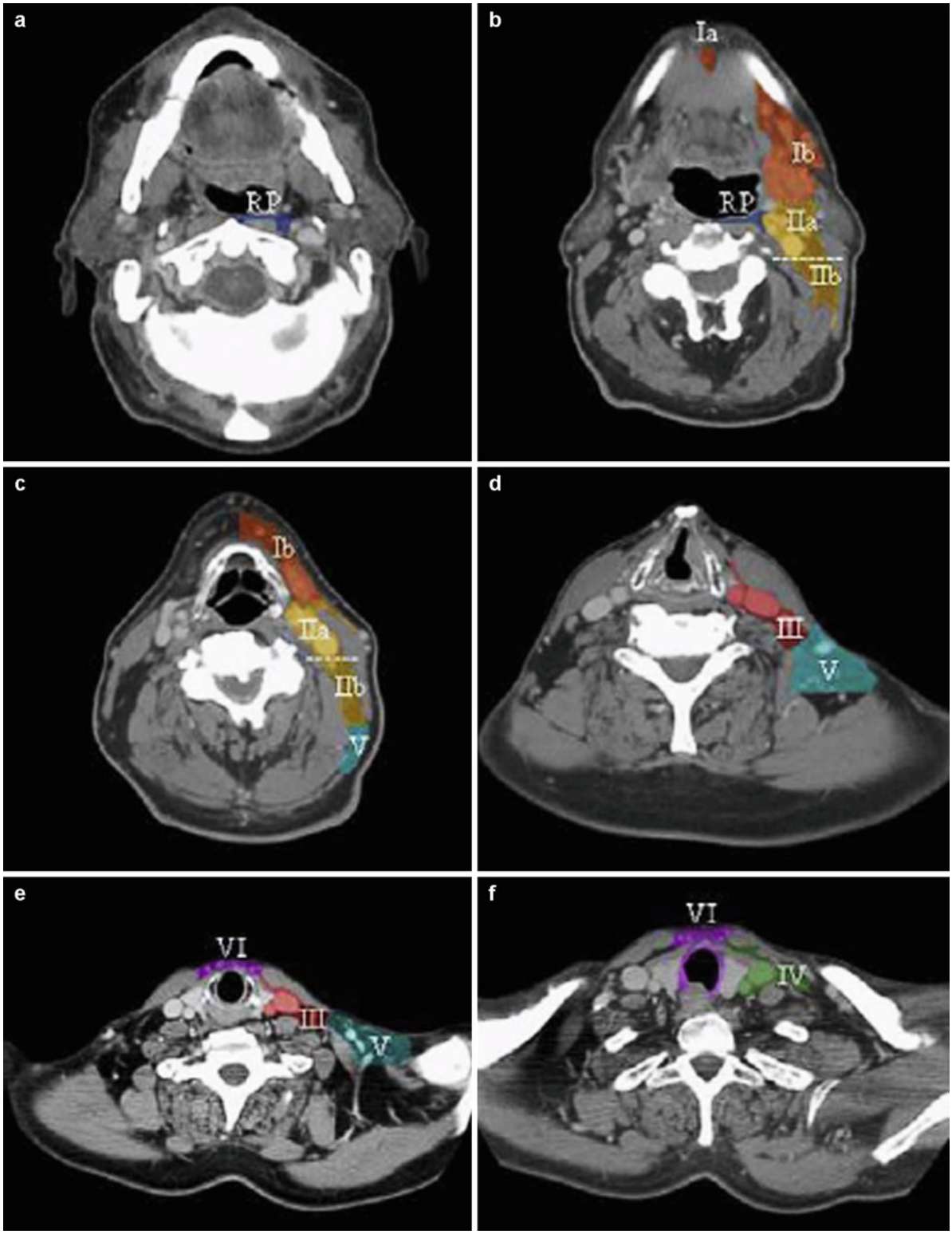

Fig. 17.2 (**a**) Parapharyngeal (**b**) Level IIa+IIb : jugular LN (**c**-**d**) Level III , IV: jugular LN (**e**-**f**) Level V: supraclavicular LN, level VI: LN around the thyroid gland

The EBV protein, latent membrane protein 2A (LMP2A), is expressed in NPC and can modulate epithelial proliferation, transformation, and differentiation and as such may promote malignancy. A key regulator of epithelial cell differentiation is the transcription factor p63, a member of the p53 family. The corresponding latent viral proteins (latent membrane protein 1 and 2) have substantial effects on cellular gene expression and cellular growth, resulting in the highly invasive, malignant growth of the carcinoma (Fotheringham et al. 2010).

Circulating free EBV DNA is commonly seen in patients with nasopharyngeal carcinoma, and the increased number of copies of EBV DNA in the blood during the initial phase of radiotherapy suggests that the viral DNA was released into the circulation after cell death (Hong et al. 2004).

The quantities of EBV DNA copies before and after treatment are significantly related to the rates of overall and disease-free survival. Several studies have reported that the levels of posttreatment EBV DNA compared with pretreatment EBV DNA are good predictors of progression-free survival (Wagner et al. 2009; Hong et al. 2004).

17.5.2 Structure of EBV and Its Genome

Epstein–Barr virus (EBV)-encoded RNA signal is present in all nasopharyngeal carcinoma cells, and early diagnosis of the disease is possible through the detection of raised antibodies against EBV. The quantity of EBV DNA detected in blood indicates the stage and prognosis of the disease. With regard to the clinical data, EBER expression in NPC was shown to be a strong independent predictor of overall and progression-free survival. Recently, it has been shown that miRNA dysregulation is implicated in the carcinogenesis of many human cancers. In cancer cells, the upregulated/downregulated miRNA could function as oncogenic/tumor-suppressing modulators. In the case of NPC, however, the critical miRNA changes involved in its carcinogenesis are not yet clearly defined (Sengupta et al. 2008).

17.5.3 EBV DNA

Circulating free EBV DNA can be detected by polymerase chain reaction (PCR) in patients (Mutirangura et al. 1998). A significant EBV DNAemia in plasma but not in cellular compartments of the peripheral blood was investigated. The EBV DNA is directly released from the tumor tissue. Ninety-five percent of patients are positive for EBV DNA in plasma at diagnosis. Moreover, the course of EBV DNA in plasma reflects the course of the disease:

Patients receiving complete remissions become negative for EBV DNA in plasma, whereas patients with persistent or progressive disease remain positive or even show increasing EBV DNA concentrations in their plasma.

The increased number of copies of EBV DNA found in the blood during the initial phase of therapy suggests that the viral DNA was released into the circulation after cell death (Leung et al. 2003). For the detection of distant metastases, the use of serum EBV DNA has been shown to be more sensitive and reliable than other options. The quantities of EBV DNA copies before and after treatment are significantly related to the rates of overall and disease-free survival (Chan et al. 2003). There was a study reporting that the levels of posttreatment EBV DNA when compared with pretreatment EBV DNA had a better prediction for progression-free survival (Lin et al. 2004).

17.5.4 VCA IgA

EBV-VCA-IgA antibodies have been identified as diagnostic and EBV-DNA in the serum or plasma as diagnostic and prognostic markers for NPC, high titers during diagnosis and with relapse is found very specific. The rise in IgA titers to these antigens can be noticed before the development of NPC and correlates with tumor burden, remission, and recurrence Therefore, this method of measuring patients' EBV-specific IgA antibodies is useful in screening for early detection of NPC (Leung et al. 2004; Li et al. 2010; Cohen et al. 2008).

17.5.5 EA (Early Antigen) IgA

Seventy percent of the patients with NPC exhibit an anti-I/O antibody of the IgA type; this is in contrast to only 3% of the patients with other malignancies. IgA can contribute to the diagnostic identification of an NPC of the undifferentiated type and/or for the proof of a relapse even before the occurrence of a clinical manifestation (Cai et al. 2010).

17.5.6 Ultrasound

US should widely be used as the initial imaging technique in the assessment of extracranial head and neck masses in children.

The frequent superficial location of head and neck tumors make them readily accessible to US examination. Technical developments in high-resolution gray-scale (B-mode) ultrasound have improved the ability of US to characterize the internal architecture of masses, beyond simply distinguishing cystic from solid lesions (Leung et al. 1991). The additional use of color Doppler ultrasound (CDUS) and power Doppler allow assessment of vascularity within the lesion, particularly helpful in the assessment of hemangioma and vascular malformations and also contributory in the assessment of enlarged lymph nodes (Imhof et al. 2004).

17.5.7 Computed Tomography

Computed tomography (CT) technology allows rapid and detailed examination of the entire neck with the ability to produce multiplanar reformatted images.

Assuming the airway is not compromised, the child should be scanned supine with the neck in the neutral position.

The region scanned extends from the top of the sphenoid sinus to the sternoclavicular joints. A bone algorithm, in addition to a standard soft tissue algorithm, is particularly important for tumors that may involve the skull base. The presence of calcification or fat within the lesion is well demonstrated on CT and helps with lesion characterization. Intravenous contrast administration is mandatory to delineate the mass, or lymphadenopathy, from adjacent normal structures. Enhancement patterns may be helpful in characterizing some masses, such as vascular tumors (Cellai et al. 1990; Yabuuchi et al. 2002; Lloyd and McHugh 2010).

17.5.8 Magnetic Resonance Imaging

The superior soft tissue resolution of MRI makes it an excellent modality in imaging of head and neck masses. It is particularly useful in delineating intracranial extension of disease. The examination is performed with the child supine in quiet respiration. Standard examination should include a T2-weighted fast spin echo (FSE) sequence in axial and coronal planes, a T2-weighted fat suppression or inversion recovery sequence, and a plain T1-weighted FSE or spin echo (SE) sequence (Lloyd and McHugh 2010). In evaluating mass lesions, a further fat-saturated T1-weighted SE sequence following gadolinium administration will often improve characterization of the mass. Additional diffusion-weighted imaging appears to also have a role in characterizing head and neck masses. A recent study found a significant difference in apparent diffusion coefficients (Olmi et al. 1995; Dillon et al. 1984).

17.5.9 Positron Emission Tomography

The increasing availability of PET-CT allows improved localization and definition of disease activity. The role of PET and PET-CT in childhood malignancies continues to be defined, but it is widely used in the staging and follow-up of lymphoma and may also have a role in soft tissue (Xie et al. 2010; Yen et al. 2009; Nakamoto et al. 2003).

17.6 Therapy

17.6.1 Chemotherapy

The mean survival rate of patients suffering from nasopharyngeal carcinoma ranges between 24% and 90%, depending on the tumor stage. While modern radiotherapy like IMRT achieves good local control, distant metastases become the predominant pattern of failure, especially among those with locoregionally advanced disease. NPC is also chemosensitive. There is a long history of clinical studies investigating combined radiotherapy (RT) and chemotherapy for NPC. Most of the early studies in pediatric patients with NPC were nonrandomized (Harrison et al. 1991; Turner and Tiver 1993; Chan et al. 1995; Teo et al. 1995; Garden et al. 1996; Lee et al. 2009). Randomized trials on combined chemotherapy and RT for NPC are reported in adult patients only (Rossi et al. 1988; Chan et al. 1995; International Nasopharynx Cancer Study Group 1996; Garden et al. 1996; Chen et al. 2008). However, randomized multi-institutional studies are necessary to standardize the treatment of the NPC in childhood. Each trial used a different approach with respect to drug combination, time sequence of chemotherapy and RT, and RT technique and dose. In the early trials, induction chemotherapy is the most often

studied approach (Chua et al. 1998; Wee et al. 2005; Lee et al. 2005; International Nasopharynx Cancer Study Group 1996). The rationale for induction chemotherapy is to reduce locoregional tumor load before start of RT and also early use of systemic treatment for eradication of micrometastases.

A recently published meta-analysis of chemotherapy in nasopharyngeal carcinoma included eight randomized trials which had completed accrual before end of 2001 and thus excluded the more recent trials from Asia. In the meta-analysis, there were four trials that investigated induction chemotherapy (+ adjuvant chemotherapy in one trial), three trials that investigated concurrent chemoradiotherapy (+ adjuvant chemotherapy in two trials), and one trial that investigated adjuvant chemotherapy alone. Overall, an absolute survival benefit of 6% at 5 years from addition of chemotherapy was observed (from 56% to 62%). A significant interaction was observed between the timing of chemotherapy and overall survival, with the highest benefit resulting from concurrent chemoradiation. The results concur with findings from meta-analysis on other head and neck cancers also (Baujat et al. 2006). Two of the four neoadjuvant studies reported improvement in relapse-free and in overall survival. The others reported no improvement generally (Pignon et al. 2009).

A pivotal study was reported by the Head and Neck Intergroup in 1998, using concurrent RT with cisplatin (100 mg/sqm D1, 22, 43) followed by adjuvant cisplatin and 5-fluouracil (5-FU) (cisplatin 80 mg/sqm D1 and 5-FU 1,000 mg/sqm/D, D1-4, Q4 weeks cycles for 3 cycles). Compared with RT alone, chemoradiation significantly improved progression-free survival and overall survival. The pattern of disease failure showed reduction of both locoregional and distant failure with chemoradiation (Al-Sarraf et al. 1998).

In contrast to the trials of NPC in adults, the neoadjuvant chemotherapy was often favored in treatment of NPC of childhood. In 2005, Rodriguez et al. published a successful series of 19 patients with NPC treated with four courses of neoadjuvant chemotherapy and irradiation (Rodriguez-Galindo et al. 2005). The Society for Pediatric Oncology and Hematology (GPOH) developed uniform therapy concepts for the treatment of NPC in Germany with children and young people from Germany, Austria, and Switzerland, including Dutch Oncology Group, and thus obtained excellent healing rates. In the NPC-91-GPOH and NPC-2003-GPOH, all juvenile patients are to be treated. High-risk patients received neoadjuvant chemotherapy consisted of cisplatin (CDDP) 100 mg/m^2 d1 and 5-fluorouracil (5-FU) 1,000 mg/m^2 daily 1–5. After three courses and irradiation, a recombinant or nature interferon β were given over a half year. The 9-year disease-free survival for patients treated on this study was 91% (Mertens et al. 2005).

Because of the rarity of this disease in children, only a multi-institutional trial may result in an improved treatment strategy. In the follow-up study NPC-2003-GPOH, the dose of radiotherapy was reduced in patients with an effective neoadjuvant chemotherapy.

The use of concurrent or, and especially, neoadjuvant chemotherapy with radiation therapy has significantly improved the outcome of advanced nasopharyngeal cancers. Because of the rarity of NPC, there are almost no reported multicenter studies for the treatment of NPC in children.

17.6.2 Radiotherapy

Radiotherapy is still the standard therapy of NPC. The major limitations of conventional 2D radiotherapy for NPC can now be overcome with three-dimensional (3D) conformal radiotherapy and IMRT. IMRT is an advanced form of 3D conformal radiotherapy, conforming high dose to tumor while conforming low dose to normal tissues (Wu et al. 2004).

IMRT planning and dose optimization is fully computerized, a process known as inverse planning, thus, it is much preferred over the more expertise-dependent forward planning in 3D conformal radiotherapy (Hsiung et al. 2002).

The use of IMRT in treatment of NPC has multiple advantages. IMRT can be used for organ preservation, e.g., sparing the parotids of high-dose radiation will preserve salivary function after radiotherapy. IMRT can achieve good dose differential between the tumor and the dose-limiting organs and thus can achieve a high dose in the tumor without overdosing the normal organs. As the fractional dose will affect the biological effectiveness of radiation, there is a component of biological modulation of radiation besides just modulating the physical radiation dose in IMRT (Withers and Thames 1988).

Simultaneous modulated accelerated radiotherapy (SMART) employs this principle for accelerated radiotherapy with IMRT. IMRT resolves the problem of dose uncertainty at the junction between the primary tumor and neck lymphatic target volumes in conventional radiotherapy (Cheng et al. 2001).

Different series reported excellent local control of more than 90% in NPC achieved with IMRT, even among patients with advanced T3-4 diseases (Pow et al. 2006). Reports also showed preservation of salivary function and improve quality of life of survivors after IMRT (Wu et al. 2004). A series of cases in which hypofractionated radiotherapy was used in combination with conventional 2D radiotherapy produced a 60% actuarial risk of complication and a 28% risk of neurological complications (Kam et al. 2007; Butler et al. 1999; Wolden et al. 2006). Cutting down late complications of treatment should be one of the main objectives of future clinical trials.

All patients in the NPC-2009-GPOH study received irradiation according to the guidelines of the study. The patients are treated with IMRT to the primary tumor, including the base of the skull and the regional lymphoid areas. In high-risk patients, the supraclavicular region should be treated by single anterior portal with a midline block at 45 Gy and the base of skull was included in the target volume. The dose to the spinal cord is limited to 40 Gy. Radiotherapy is delivered daily in single doses of 1.8 Gy. All primary tumor-bearing areas are given an additional dose of 14.4 Gy to a total dose of 59.4 Gy. In the stage II patient, the nasopharynx and regional lymph nodes are irradiated with 45 Gy and the pituitary gland is excluded.

17.6.3 Interferon Therapy

The combination of cisplatin and 5-fluorouracil in combination with radiotherapy is the most widely used therapy regimen for nasopharyngeal carcinomas. In addition, β-interferon is also only used in the German study.

In the German study NPC-91-GPOH and NPC-2003-GPOH, all patients underwent 6 months of recombinant IFN-beta or native IFN-beta treatment after completion of radiation therapy, receiving a dose of 10^5 U per kg body weight (max dose 6×10^6 U) intravenously three times a week. It is a nonrandomized study with a good result of 90%.

17.7 Metastasis

The NPC usually metastasizes lymphatics but also has hematogenous spread. The lymphatic spread is initially described by Frommonhold and Grauwerk as rear upper rail and drainage flows into the lymph nodes of the intersection group, which is partly located behind the posterior edge of C2 vertebral body (Frommhold and Gauwerk 1972). The high number of metastases, despite sufficient local therapy, represents a major problem in the treatment of NPC. The development of metastases occurred early, usually in the first 2 years after diagnosis, and is the most important factor of risk for the survival of patients.

Despite the use of chemoradiotherapy, distant metastases remain the major cause of failure, especially in stage IV patients. However, induction chemotherapy showed significant reduction of distant failures. Thus, there is now revival of interest in using induction and concurrent chemotherapy in treatment of NPC (Cheng et al. 2000).

17.8 New Treatment Strategies

17.8.1 T Cell Therapy

EBV-specific cytotoxic T cell (CTL) lines can readily be generated from individuals with NPC, notwithstanding the patients' prior exposure to chemotherapy/radiation. In a pilot study, patients diagnosed with advanced NPC were treated with autologous CTLs. All patients tolerated the CTLs, although one developed increased swelling at the site of preexisting disease. The administration of EBV-specific CTLs to patients with advanced NPC was feasible, appears to be safe, and could be associated with significant antitumor activity.

The EBV-specific CTLs used in this study were reactivated using LCLs that express all EBV latent antigens. LCLs are excellent antigen-presenting cells that are readily available for all patients, as only a limited amount of blood are required to establish an LCL line. As expected using this method, only a minority of the infused lines contained cytotoxic T cells specific for LMP2 (an EBV antigen usually expressed by NPC tumor cell mononuclear cells). Although there was no persistent rise in the frequency of circulating T cells

specific for LMP2 after infusion, the CTLs appeared to show significant anti-tumor activity.)

The EBV-specific CTLs were biologically active in vivo, reducing levels of EBV DNA in peripheral blood (Louis et al. 2010; Comoli et al. 2005).

Another approach to reduce distant failure is by adding targeted therapy to chemotherapy. In a recently closed phase II trial (RTOG 0615), bevacizumab (a monoclonal antibody directed against vascular endothelial growth factor) was added to the concurrent and adjuvant phases of therapy.(Louis et al. 2010) It was hoped that adding on antiangiogenic agents to the chemotherapy can destroy distant micrometastases in primary treatment. Finally, the antitumor effect of taxanes has been shown in several studies in adult NPC, and its incorporation into the frontline management of this malignancy may provide additional cure options (Radiation Therapy Oncology Group of the American College of Radiology 2006).

17.9 Long-Term Sequelae

Survivors of NPC following radiotherapy or chemoradiation have impaired the health-related quality of life. Patients may suffer from a variety of late complications, many of which result from the effects of radiation on the dose-limiting organs situated adjacent to the nasopharynx and cervical lymph node (Huang et al. 1994). NPC survivors almost uniformly develop hypothyroidism secondary to neck irradiation and also are at risk for panhypopituitarism resulting from pituitary damage. A close endocrine follow-up is thus required for early diagnosis and intervention (Fang et al. 2002). Ototoxicity is also very common, and its incidence is particularly higher in patients receiving chemotherapy in addition to radiation, which often involved the auditory apparatus. A small proportion of the long-term sequelae represent the effects of unhealed residual damage by the tumor, such as residual cranial nerve palsies and serous otitis media resulting from persistent disturbance of the Eustachian tube function (McMillan et al. 2004).

In up to 8,5% of the NPC patients, subsequent malignancies developed 8.6–27 years after NPC diagnosis. The 15-year cumulative incidence of any morbidity, sensorineural hearing loss, primary hypothyroidism, and growth hormone deficiency related to the stage were 84%, 53%, 43% and 14%, respectively. There are dose-response relationships between RT dose and primary hypothyroidism and growth hormone deficiency (Ulger et al. 2007).

17.10 Juvenile Nasopharyngeal Angiofibroma

17.10.1 Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is a rare tumor with prominent vascularity and *benign histological* features. It originates from the superior margin of the sphenopalatine foramen, which is also a route for the sphenopalatine artery branching from the internal maxillary artery (Schuon et al. 2007; Tosun et al. 2006).

The reported incidence is between 1 in 6,000 and 1 in 60,000 otolaryngology patients and accounts for 0.5% of all head and neck neoplasms (Mann et al. 2004; Glad et al. 2007). JNA accounts for 0.5% of all head and neck neoplasms, and it is considered to be the most common benign neoplasm of the nasopharynx. Evidence of intracranial spread occurs in 10–20% of cases. The average age at onset of symptoms is 15 years (Midilli et al. 2009; Paris et al. 2001).

Although histologically benign in appearance, JNAs are locally aggressive and destructive, spreading from the nasal cavity to the nasopharynx, paranasal sinuses, and orbit skull base with intracranial extension. The pathogenesis of JNA is unknown.

The tumor may grow towards the nasal fossa and extend to the posterior portion of the middle turbinate, which becomes a common part of the tumor mass. The angiofibroma may extend laterally towards the pterygomaxillary fossa and destroy the posterior wall of the maxillary sinus. Eventually, the tumor may invade the intratemporal fossa and the middle cranial fossa. This is a general view of the growth of this tumor. The actual modes of invasion into local structures may be unpredictable and far from a typical pattern (Paris et al. 2001; Marshall and Bradley 2006).

17.10.2 Symptoms

The most common presenting symptom is persistent nasal obstruction with repetitive epistaxis.

Further classical clinical presentation is unilateral nasal block and/or rhinorrhea, and occasionally pain. Because of its invasive nature, the tumor may cause facial deformity and proptosis, changes in visual acuity, and cranial nerve palsy if it reaches the orbit and intracranial region (Weprin and Siemers 1991; Tyagi et al. 2007).

17.10.3 Pathogenesis

The gender selectivity of JNA*, with a high male-to-female ratio,* and the relatively young age at diagnosis suggest hormone-dependent development. Hormonal disorders have been reported in patients with JNA, and androgen and estrogen receptors have been identified in tumor tissue; however, a hormonal influence on JNA is controversial. Recent studies have attempted to further delineate the pathogenesis of JNA through analysis of genetic and molecular changes. While JNA is known to be sensitive to androgens, there are likely intermediary cytokines and/or growth factors that mediate aggressive stoma cell proliferation and angiogenesis. Transforming growth factor beta1 (TGF-beta1) is a polypeptide that is secreted in an inactive form, cleaved to produce an active form, and then deactivated in the tissues. The localization of activated TGF-beta1 to the fibroblasts and endothelial cells within JNA tumors suggests that TGF-beta1 may play a role in the stromal cell proliferation and angiogenesis associated with JNA. The expression of estrogen receptor beta by the tumor cells recently has been demonstrated (Lee et al. 1980; Liang et al. 2000; Saylam et al. 2006; Ngan et al. 2008; Zhang et al. 2003).

17.10.4 Diagnosis

The diagnosis of JNA is based on a precise clinical history and examination of the patient, and imaging (CT or MRI). Tissue biopsies should be avoided due to the highly vascular nature of the tumor. Angiography is used to define the feeding arteries of the tumor and to provide information for embolization (Nicolai et al. 2003; Jacobsson et al. 1989).

JNA is classified as Type I when the tumor is restricted to the nasal cavity and the nasopharynx without bone destruction; Type II when the tumor invades the pterygomaxillary fossa and maxillary, sphenoidal, and ethmoid sinuses with bone destruction; Type III when the tumor invades the intratemporal fossa, the orbit, and the parasellar region but remaining lateral to the cavernous sinus; and Type IV when the tumor invades the cavernous sinus, the optic chiasma, and the pituitary fossa (Howard et al. 2001).

Andrews staging system for juvenile nasopharyngeal angiofibroma (1989)

Stage	
I	Tumor limited to the nasal cavity and nasopharynx
II	Tumor invading the pterygopalatine fossa or maxillary, ethmoidal, and sphenoid sinuses; with bone destruction
III	Tumor invading the infratemporal fossa or orbital region: (a) Without intracranial involvement and (b) With extradural intracranial involvement
IV	Tumor with intradural intracranial involvement: (a) Without or (b) with infiltration of cavernous sinus, pituitary fossa, or optic chiasma

17.10.5 Therapy

The management of JNA has changed during the last decades. It is generally agreed that surgery is the treatment of choice for JNA. Preoperative selective arterial embolization is almost always indicated as it helps decrease the risk of intraoperative hemorrhage and facilitates the resection of large tumors. The management of JNA should be planned by an experienced head and neck surgeon, as part of a multidisciplinary team, preferably in a tertiary referral setting. Surgery aims for a complete and safe resection of tumor, with minimal morbidity and loss of blood. A transpalatal, transmaxillar (lateral rhinotomy or midfacial approach) is usually performed (Dubey and Molumi 2007; Belmont 1988).

For stages I and II, a transpalatal approach results in good outcome when the lesion is limited to the nasal cavity, nasopharynx, and paranasal sinuses. For patients with intracranial extension, the LeFort I surgical technique should be used. Involvement of the orbit, middle cranial fossa, and base of the pterygoid by the primary JNA results in a higher incidence of recurrent tumor (Borghei et al. 2006; Yiotakis et al. 2008).

Recurrence rates as high as 50% (ranging from 6% to 50%) have been reported (Reddy et al. 2001). During the last decade, the increased understanding of

angiogenesis has allowed the development of new therapeutic approaches. Since strong vascularity is a common feature of JNAs, it has been suggested that antiangiogenic therapies ought to be considered in the management of selected cases (Hashizume et al. 2010). Other methods that have been used as primary treatment include hormone therapy, chemotherapy, and radiotherapy.

References

Ali H, al-Sarraf M (2000) Chemotherapy in advanced nasopharyngeal cancer. Oncology 14(8):1223–1230

Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, Forastiere AA, Adams G, Sakr WA, Schuller DE, Ensley JF (1998) Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 16(4):1310–1317

Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT et al (2006) Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys 64(1):47–56

Belmont JR (1988) The Le Fort I osteotomy approach for nasopharyngeal and nasal fossa tumors. Arch Otolaryngol Head Neck Surg 114:751–754

Borghei P, Baradaranfar MH, Borghei SH, Sokhandon F (2006) Transnasal endoscopic resection of juvenile nasopharyngeal angiofibroma without preoperative embolization. Ear Nose Throat J 85:740–743, 746

Bornkamm GW (1984) Virologisch-serologische Diagnostik des Nasopharynxkarzinoms. In Nasopharynx-Tumoren. Urban & Schwarzenberg, München-Wien-Baltimore, pp 15–21

Bray F, Haugen M et al (2008) Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiologic implications. Cancer Epidemiol Biomarkers Prev 17(9):2356–2365

Butler EB, Teh BS, Grant WH 3rd, Uhl BM, Kuppersmith RB, Chiu JK et al (1999) Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 45(1):21–32

Cai YL, Zheng YM, Cheng JR, Wang W, Zhang YN, Wang WH, Wu YS, Zhong WM, Li J, Mo YK (2010) Relationship between clinical stages of nasopharyngeal carcinoma and Epstein-Barr virus antibodies Rta/IgG, EBNA1/IgA, VCA/IgA and EA/IgA. Nan Fang Yi Ke Da Xue Xue Bao 30(3):509–511

Cellai E, Olmi P, Chiavacci A, Giannardi G, Fargnoli R, Villari N et al (1990) Computed tomography in nasopharyngeal carcinoma: Part II: Impact on survival. Int J Radiat Oncol Biol Phys 19(5):1177–1182

Chan AT, Teo PM, Leung TW, Leung SF, Lee WY, Yeo W et al (1995) A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 33(3):569–577

Chan KH, Gu YL, Ng F, Ng PS, Seto WH, Sham JS, Chua D, Wei W, Chen YL, Luk W, Zong YS, Ng MH (2003) EBV specific antibody-based and DNA-based assays in serologic diagnosis of nasopharyngeal carcinoma. Int J Cancer 105(5):706–709

Chang ET, Adami HO (2006) The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 15(10):1765–1777

Chen Y, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL et al (2008) Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. Int J Radiat Oncol Biol Phys 71(5):1356–1364

Cheng SH, Jian JJ, Tsai SY, Yen KL, Chu NM, Chan KY et al (2000) Long-term survival of nasopharyngeal carcinoma following concomitant radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys 48(5):1323–1330

Cheng JC, Chao KS, Low D (2001) Comparison of intensity modulated radiation therapy (IMRT) treatment techniques for nasopharyngeal carcinoma. Int J Cancer 96(2):126–131

Cheuk DK, Billups CA, Martin MG, Roland CR, Ribeiro RC, Krasin MJ, Rodriguez-Galindo C (2011) Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. Cancer 117(1):197–206

Chong VF, Fan YF, Khoo JB (1996) Nasopharyngeal carcinoma with intracranial spread: CT and MR characteristics. J Comput Assist Tomogr 20(4):563–569

Chua DT, Sham JS, Choy D, Lorvidhaya V, Sumitsawan Y, Thongprasert S et al (1998) Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma: Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Cancer 83(11):2270–2283

Cohen F, Monnet O, Casalonga F, Jacquier A, Vidal V, Bartoli JM, Moulin G (2008) Nasopharyngeal carcinoma. J Radiol 89(7–8 Pt 2):956–967

Comoli P, Pedrazzoli P, Maccario R et al (2005) Cell therapy of stage IV nasopharyngeal carcinoma with autologous Epstein-Barr virus-targeted cytotoxic T lymphocytes. J Clin Oncol 23:8942–8949

Dillon WP, Mills CM, Kjos B, DeGroot J, Brant-Zawadzki M (1984) Magnetic resonance imaging of the nasopharynx. Radiology 152(3):731–738

Dittmer DP, Hilscher CJ, Gulley ML, Yang EV, Chen M, Glaser R (2008) Multiple pathways for Epstein-Barr virus episome loss from nasopharyngeal carcinoma. Int J Cancer 123(9): 2105–2112

Dubey SP, Molumi CP (2007) Critical look at the surgical approaches of nasopharyngeal angiofibroma excision and "total maxillary swing" as a possible alternative. Ann Otol Rhinol Laryngol 116:723–730

Fang FM, Chiu HC, Kuo WR, Wang CJ, Leung SW, Chen HC et al (2002) Health-related quality of life for nasopharyngeal carcinoma patients with cancer-free survival after treatment. Int J Radiat Oncol Biol Phys 53(4):959–968

Fotheringham JA, Mazzucca S, Raab-Traub N (2010) Epstein-Barr virus latent membrane protein-2A-induced DeltaNp63 alpha expression is associated with impaired epithelial-cell differentiation. Oncogene 29(30):4287–4296

Frommhold H, Gauwerk F (1972) Zur Strahlenbehandlung der Epipharynxtumoren. Strahlentherapie 144:509–514

Garden AS, Lippman SM, Morrison WH, Glisson BS, Ang KK, Geara F et al (1996) Does induction chemotherapy have a role in the management of nasopharyngeal carcinoma? Results of treatment in the era of computerized tomography. Int J Radiat Oncol Biol Phys 36(5):1005–1012

Glad H, Vainer B, Buchwald C, Petersen BL, Theilgaard SA, Bonvin P, Lajer C, Jakobsen J (2007) Juvenile nasopharyngeal angiofibromas in Denmark 1981–2003: diagnosis, incidence, and treatment. Acta Otolaryngol 127:292–299

Godtfredsen E (1944) Chapter III: on the histopathology of malignant nasopharyngeal tumours. Acta Pathol Microbiol Scand 32(Suppl 59):38–56

Gulley ML (2001) Molecular diagnosis of Epstein-Barr-virus-related diseases. J Mol Diagn 3(1):1–10

Harrison LB, Pfister DG, Bosl GJ (1991) Chemotherapy as part of the initial treatment for nasopharyngeal cancer. Oncology (Williston Park) 5(2):67–70

Hashizume H, Falcon BL, Kuroda T, Baluk P, Coxon A, Yu D, Bready JV, Oliner JD, McDonald DM (2010) Complementary actions of inhibitors of Angiopoietin-2 and VEGF on tumor angiogenesis and growth. Cancer Res 70:2213–2223

Hildesheim A, Apple RJ, Chen CJ, Wang SS, Cheng YJ, Klitz W, Mack SJ, Chen IH, Hsu MM, Yang CS, Brinton LA, Levine PH, Erlich HA (2002) Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 94(23):1780–1789

Hong RL, Lin CY, Ting LL, Ko JY, Hsu MM (2004) Comparison of clinical and molecular surveillance in patients with advanced nasopharyngeal carcinoma after primary therapy: the potential role of quantitative analysis of circulating Epstein-Barr virus DNA. Cancer 100(7):1429–1437

Howard DJ, Lloyd G, Lund V (2001) Recurrence and its avoidance in juvenile angiofibroma. Laryngoscope 111: 1509–1511

Hsiung CY, Yorke ED, Chui CS, Hunt MA, Ling CC, Huang EY et al (2002) Intensity-modulated radiotherapy versus conventional three-dimensional conformal radiotherapy for boost or salvage treatment of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 53(3):638–647

Huang TS, Huang SC, Hsu MM (1994) A prospective study of hypothalamus pituitary function after cranial irradiation with or without radiosensitizing chemotherapy. J Endocrinol Invest 17(8):615–623

Imhof H, Czerny C, Hormann M, Krestan C (2004) Tumors and tumorlike lesions of the neck: from childhood to adult. Eur Radiol 14:L155–L165

Institute Gustave Roussy, Rue Camille Desmoulins, Villejuif, France (1996) Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV(> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. VUMCA I trial. Int J Radiat Oncol Biol Phys 35(3):463–469

Jacobsson M, Petruson B, Ruth M, Svendsen P (1989) Involution of juvenile nasopharyngeal angiofibroma with intracranial extension. A case report with computed tomographic assessment. Arch Otolaryngol Head Neck Surg 115:238–239

Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F et al (2007) Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 25(31):4873–4879

King AD, Ma BB, Yau YY, Zee B, Leung SF, Wong JK, Kam MK, Ahuja AT, Chan AT (2008) The impact of 18F-FDG PET/CT on assessment of nasopharyngeal carcinoma at diagnosis. Br J Radiol 81(964):291–298

Krueger GRF, Wustrow J (1981) Current classification of nasopharyngeal carcinoma at Cologne University. In: Grundmann E, Krueger GRF, Ablashi DV (eds) Nasopharyngeal carcinoma, vol 5. Gustav Fischer Verlag, Stuttgart, pp 11–15

Lee DA, Rao BR, Meyer JS, Prioleau PG, Bauer WC (1980) Hormonal receptor determination in juvenile nasopharyngeal angiofibromas. Cancer 46:547–551

Lee AW, Poon YF, Foo W, Law SC, Cheung FK, Chan DK et al (1992) Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys 23(2):261–270

Lee AW, Foo W, Law SC, Poon YF, Sze WM OSK, Tung SY, Lau WH (1997) Nasopharyngeal carcinoma: presenting symptoms and duration before diagnosis. Hong Kong Med J 3(4):355–361

Lee AW, Foo W, Law SC et al (1999) Staging of nasopharyngeal carcinoma: from Ho's to the new UICC system. Int J Cancer 84:179–187

Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L et al (2005) Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 23(28):6966–6975

Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P et al (2009) Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol 27(22):3684–3690

Leung SF, Metreweli C, Tsao SY, Van Hasselt CA (1991) Staging abdominal ultrasonography in nasopharyngeal carcinoma. Australas Radiol 35(1):31–32

Leung SF, Chan AT, Zee B, Ma B, Chan LY, Johnson PJ et al (2003) Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type. Cancer 98(2):288–291

Leung SF, Tam JS, Chan AT, Zee B, Chan LY, Huang DP et al (2004) Improved accuracy of detection of nasopharyngeal carcinoma by combined application of circulating Epstein-Barr virus DNA and anti-Epstein-Barr viral capsid antigen IgA antibody. Clin Chem 50(2):339–345

Li S, Deng Y, Li X, Chen Q, Liao XC, Qin X (2010) Diagnostic value of Epstein-Barr virus capsid-IgA in nasopharyngeal carcinoma: a meta-analysis. Chin Med J (Engl) 123(9):1201–1205

Liang J, Yi Z, Lianq P (2000) The nature of juvenile nasopharyngeal angiofibroma. Otolaryngol Head Neck Surg 123: 475–481

Liebowitz D (1994) Nasopharyngeal carcinoma: the Epstein-Barr virus association. Semin Oncol 21(3):376–381

Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS et al (2004) Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med 350(24):2461–2470

Lloyd C, McHugh K (2010) The role of radiology in head and neck tumours in children. Cancer Imaging 10:49–61

Lo YM, Leung SF, Chan LY, Chan AT, Lo KW, Johnson PJ et al (2000) Kinetics of plasma Epstein-Barr virus DNA during radiation therapy for nasopharyngeal carcinoma. Cancer Res 60(9):2351–2355

Louis CU, Straathof K, Bollard CM et al (2010) Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. J Immunother 33:983–990

Mann WJ, Jecker P, Amedee RG (2004) Juvenile angiofibromas: changing surgical concept over the last 20 years. Laryngoscope 114:291–293

Marks JE, Phillips JL, Menck HR (1998) The National Cancer Data Base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. Cancer 83(3):582–588

Marshall AH, Bradley PJ (2006) Management dilemmas in the treatment and follow-up of advanced juvenile nasopharyngeal angiofibroma. ORL J Otorhinolaryngol Relat Spec 68:211–216

McMillan AS, Pow EH, Leung WK, Wong MC, Kwong DL (2004) Oral health-related quality of life in southern Chinese following radiotherapy for nasopharyngeal carcinoma. J Oral Rehabil 31(6):600–608

Mertens R, Granzen B, Lassay L, Gademann G, Hess CF, Heimann G (1997) Nasopharyngeal carcinoma in childhood and adolescence: concept and preliminary results of the cooperative GPOH study NPC-91. Gesellschaft für Pädiatrische Onkologie und Hämatologie. Cancer 80(5):951–959

Mertens R, Granzen B, Lassay L, Bucsky P, Hundgen M, Stetter G, Heimann G, Weiss C, Hess CF, Gademann G (2005) Treatment of nasopharyngeal carcinoma in children and adolescents: definitive results of a multicenter study (NPC-91-GPOH). Cancer 104(5):1083–1089

Micheau C, Rilke F, Pilotti S (1978) Proposal for a new histopathological classification of the carcinomas of the nasopharynx. Tumori 64(5):513–518

Midilli R, Karci B, Akyildiz S (2009) Juvenile nasopharyngeal angiofibroma: analysis of 42 cases and important aspects of endoscopic approach. Int J Pediatr Otorhinolaryngol 73:401–408

Mutirangura A, Pornthanakasem W, Theamboonlers A, Sriuranpong V, Lertsanguansinchi P, Yenrudi S, Voravud N, Supiyaphun P, Poovorawan Y (1998) Epstein-Barr viral DNA in serum of patients with nasopharyngeal carcinoma. Clin Cancer Res 4(3):665–669

Nakamoto Y, Osman M, Wahl RL (2003) Prevalence and patterns of bone metastases detected with positron emission tomography using F-18 FDG. Clin Nucl Med 28(4): 302–307

Ngan BY, Forte V, Campisi P (2008) Molecular angiogenic signaling in angiofibromas after embolization: implications for therapy. Arch Otolaryngol Head Neck Surg 134:1170–1176

Nicolai P, Berlucchi M, Tomenzoli D, Cappiello J, Trimarchi M, Maroldi R, Battaglia G, Antonelli AR (2003) Endoscopic surgery for juvenile angiofibroma: when and how. Laryngoscope 113:775–782

Niedobitek G, Young LS (1994) Epstein-Barr virus persistence and virus-associated tumors. Lancet 343:333–335

Olmi P, Fallai C, Colagrande S, Giannardi G (1995) Staging and follow-up of nasopharyngeal carcinoma: magnetic resonance imaging versus computerized tomography. Int J Radiat Oncol Biol Phys 32(3):795–800

Ozyar E, Atahan IL, Akyol FH, Gurkaynak M, Zorlu AF (1994) Cranial nerve involvement in nasopharyngeal carcinoma: its prognostic role and response to radiotherapy. Radiat Med 12(2):65–68

Paris J, Guelfucci B, Moulin G, Zanaret M, Triglia JM (2001) Diagnosis and treatment of juvenile nasopharyngeal angiofibroma. Eur Arch Otorhinolaryngol 258:120–124

Pignon JP, le Maitre A, Maillard E, Bourhis J (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92(1):4–14

Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH et al (2006) Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 66(4):981–991

Raab-Traub N (2002) Epstein-Barr virus in the pathogenesis of NPC. Semin Cancer Biol 12:4310

Radiation Therapy Oncology Group of the American College of Radiology (2006) A phase II study of concurrent chemoradiotherapy using three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiation therapy (IMRT) + bevacizumab (BV) for locally or regionally advanced nasopharyngeal cancer. Radiation therapy oncology group, principal investigator : Nancy Lee, MD www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=7157

Reddy KA, Mendenhall WM, Amdur RJ, Stringer SP, Cassisi NJ (2001) Long-term results of radiation therapy for juvenile nasopharyngeal angiofibroma. Am J Otolaryngol 22:172–175

Ren ZF, Liu WS, Qin HD, Xu YF, Yu DD, Feng QS, Chen LZ, Shu XO, Zeng YX, Jia W (2010) Effect of family history of cancers and environmental factors on risk of nasopharyngeal carcinoma in Guangdong, China. Cancer Epidemiol 34(4): 419–424

Rodriguez-Galindo C, Wofford M, Castleberry RP, Swanson GP, London WB, Fontanesi J, Pappo AS, Douglass EC (2005) Preradiation chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma. Cancer 103(4):850–857

Rossi A, Molinari R, Boracchi P, Del Vecchio M, Marubini E, Nava M et al (1988) Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. J Clin Oncol 6(9): 1401–1410

Saylam G, Yucel OT, Sungur A, Onerci M (2006) Proliferation, angiogenesis and hormonal markers in juvenile nasopharyngeal angiofibroma. Int J Pediatr Otorhinolaryngol 70: 227–234

Schuon R, Brieger J, Heinrich UR, Roth Y, Szyfter W, Mann WJ (2007) Immunohistochemical analysis of growth mechanisms in juvenile nasopharyngeal angiofibroma. Eur Arch Otorhinolaryngol 264:389–394

Sengupta S, den Boon JA, Chen IH, Newton MA, Stanhope SA, Cheng YJ, Chen CJ, Hildesheim A, Sugden B, Ahlquist P (2008) MicroRNA 29c is down-regulated in nasopharyngeal carcinomas, up-regulating mRNAs encoding extracellular matrix proteins. Proc Natl Acad Sci USA 105(15): 5874–5878

Sham JS, Cheung YK, Choy D, Chan FL, Leong L (1991) Nasopharyngeal carcinoma: CT evaluation of patterns of tumor spread. AJNR Am J Neuroradiol 12(2):265–270

Shanmugaratnam K (1980) Nasopharyngeal carcinoma: epidemiology, histopathology and aetiology. Ann Acad Med Singapore 9(3):289–295

Sultan I, Casanova M et al (2010) Differential features of nasopharyngeal carcinoma in children and adults: a SEER study. Pediatr Blood Cancer 55(2):279–284

Tang LL, Li WF, Chen L, Sun Y, Chen Y, Liu LZ, Mao YP, Lin AH, Li L, Ma J (2010) Prognostic value and staging categories of anatomic masticator space involvement in nasopharyngeal carcinoma: a study of 924 cases with MR imaging. Radiology 257(1):151–157

Teo PM, Leung TW, Chan AT, Yu P, Lee WY, Leung SF et al (1995) A retrospective study of the use of cisplatinum-5-fluorouracil neoadjuvant chemotherapy in cervical-node-positive nasopharyngeal carcinoma (NPC). Eur J Cancer B Oral Oncol 31B(6):373–379

Tosun S, Ozer C, Gerek M, Yetiser S (2006) Surgical approaches for nasopharyngeal angiofibroma: comparative analysis and current trends. J Craniofac Surg 17:15–20

Turner SL, Tiver KW (1993) Synchronous radiotherapy and chemotherapy in the treatment of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 27(2):371–377

Tyagi I, Syal R, Goyal A (2007) Recurrent and residual juvenile angiofibromas. J Laryngol Otol 121:460–467

Ulger S, Ulger Z, Yildiz F, Ozyar E (2007) Incidence of hypothyroidism after radiotherapy for nasopharyngeal carcinoma. Med Oncol 24(1):91–94

Wagner HJ, Mertens R, Reiter A, Gauch C (2009) Molecular and serological monitoring of pediatric patients with nasopharyngeal carcinoma treated by the protocol NPC-2003-GPOH of the German Society for pediatric oncology. Pediatr Blood Cancer. 53:751

Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T et al (2005) Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 23(27):6730–6738

Wei W, St Sham J (2005) Nasopharyngeal carcinoma. Lancet 365:2041–2054

Weprin LS, Siemers PT (1991) Spontaneous regression of juvenile nasopharyngeal angiofibroma. Arch Otolaryngol Head Neck Surg 117:796–799

Withers HR, Thames HD (1988) Dose fractionation and volume effects in normal tissues and tumors. Am J Clin Oncol 11(3):313–329

Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ (2006) Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 64(1):57–62

Wong TS, Kwong DL, Sham JS, Wei WI, Kwong YL, Yuen AP (2004) Quantitative plasma hypermethylated DNA markers of undifferentiated nasopharyngeal carcinoma. Clin Cancer Res 10(7):2401–2406

Wu VW, Kwong DL, Sham JS (2004) Target dose conformity in 3-dimensional conformal radiotherapy and intensity modulated radiotherapy. Radiother Oncol 71(2):201–206

Xie P, Yue JB, Zhao HX, Sun XD, Kong L, Fu Z, Yu JM (2010) Prognostic value of 18F-FDG PET-CT metabolic index for nasopharyngeal carcinoma. J Cancer Res Clin Oncol 136(6):883–889, Pub 2009 Nov 20

Yabuuchi H, Fukuya T, Murayama S et al (2002) CT and MR features of nasopharyngeal carcinoma in children and young adults. Clin Radiol 57:205–210

Yen RF, Ting LL, Cheng MF, Wu YW, Tzen KY, Hong RL (2009) Usefulness of 201TL SPECT/CT relative to 18F-FDG PET/CT in detecting recurrent skull base nasopharyngeal carcinoma. Head Neck 31(6):717–724

Yiotakis I, Eleftheriadou A, Davilis D, Giotakis E, Ferekidou E, Korres S, Kandiloros D (2008) Juvenile nasopharyngeal angiofibroma stages I and II: a comparative study of surgical approaches. Int J Pediatr Otorhinolaryngol 72:793–800

Zhang PJ, Weber R, Liang HH, Pasha TL, LiVolsi VA (2003) Growth factors and receptors in juvenile nasopharyngeal angiofibroma and nasal polyps: an immunohistochemical study. Arch Pathol Lab Med 127:1480–1484

Esthesioneuroblastoma

18

Barbara Hero and Gianni Bisogno

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Esthesioneuroblastoma, also often called olfactory neuroblastoma, is a rare tumor thought to arise from the olfactory neuroepithelium. It may occur at any age and accounts for 1–5% of intranasal tumors with an estimated incidence of 0.4/million population (Broich et al. 1997; Ferlito et al. 2003; Thompson 2009). No sex predisposition has been reported. Recent reports favor a unimodal age distribution with the majority of patients diagnosed in the fourth and fifth decades of life (Resto et al. 2000; Ferlito et al. 2003; Jethanamest et al. 2007), but previously an additional peak of incidence in the second decade has been claimed (Elkon et al. 1979).

In children esthesioneuroblastoma is rare with an estimated incidence of 0.1/100,000 children up to 15 years, but it is the most frequent cancer of the nasal cavity in this age group, representing 28% of cases registered in a series of 47 patients below 19 years with nasal cavity tumors in the SEER database from 1973 to 2002 (Benoit et al. 2008). Only single cases have been reported in young children below 10 years of age, the youngest reported case being as young as 2 years (Woerner et al. 1986; Perkkio et al. 1991; Bobele et al. 1994; Kumar et al. 2002; Eich et al. 2005; Jethanamest et al. 2007).

The clinical and histological diagnosis of esthesioneuroblastoma is confusing, and misdiagnosis has been reported in quite substantial parts of patients, where histology was reassessed according to current immunohistochemical criteria (Hirose et al. 1995; Resto et al. 2000; Cohen et al. 2002; Eich et al. 2005). Therefore, clinical features reported in the literature should be interpreted with cautiousness if not proved in recently reported series.

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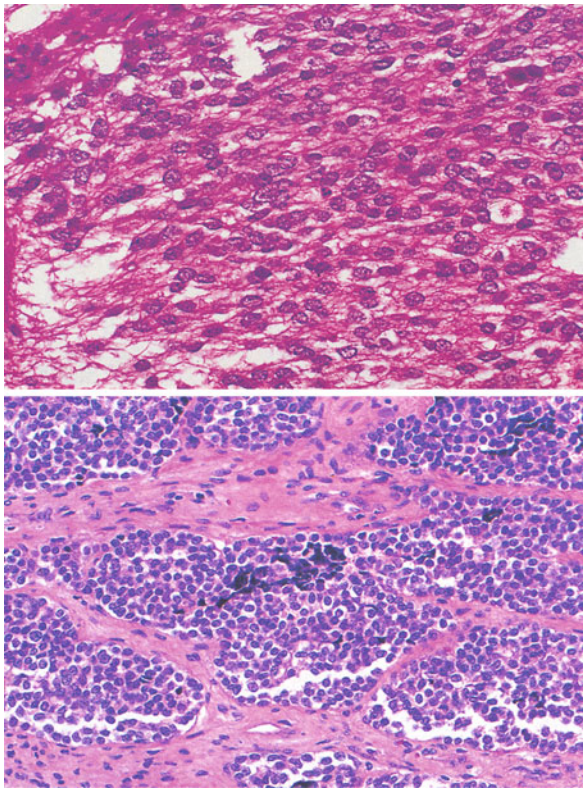

Fig. 18.1 Esthesioneuroblastoma, histology

18.1 Pathology

Esthesioneuroblastoma is a tumor with small, round, blue tumor cells arranged in a lobular architecture in neurofibrillary stroma (Fig. 18.1). Rosettes and pseudorosettes as well as calcifications may be found. Based on assessment of lobular tumor architecture, mitotic activity, nuclear pleomorphism, rosettes, and tumor necrosis, Hyams et al. proposed a grading system, which is correlated to prognosis (Hyams et al. 1988). Immunohistochemically, esthesioneuroblastoma may stain positive for synaptophysin, chromogranin, CD56, neuron-specific enolase, NFP, and S-100 protein, but negative for desmin, myogenin, leukocyte common antigen, and CD99 (reviewed in Faragalla and Weinreb 2009; Thompson 2009).

Due to the rareness of the disease, histological evaluation by a second experienced pathologist should be aimed for. Other small round cell tumors as rhabdomyosarcoma, tumors of the Ewing tumor family, neuroblastoma, lymphoma, and, less common in childhood, neuroendocrine carcinoma, squamous cell carcinoma, and sinonasal undifferentiated carcinoma, have to be ruled out. Although previously controversially discussed (Sorensen et al. 1996), it has meanwhile been shown that esthesioneuroblastoma does not belong to the Ewing tumor family, as CD99/MIC staining and the typical translocations are lacking (Nelson et al. 1995; Argani et al. 1998; Mezzelani et al. 1999). From the histopathological point of view, metastatic neuroblastoma would present with identical findings as esthesioneuroblastoma. Amplification of the MYCN oncogen, which is found in many aggressive neuroblastomas, has so far not been reported in esthesioneuroblastoma. Thus, in single cases, molecular assessment of the tumor specimen, showing Ewing tumor family typic translocations or MYCN amplification, may be helpful to rule out esthesioneuroblastoma.

18.2 Staging

The origin of esthesioneuroblastoma is confined to the olfactory mucosa involving the superior turbinate, cribriform plate, and the superior one third of the nasal cavity. It may spread into the paranasal sinuses, the orbits, and – through the lamina cribriformis – into the cranial cavity. Although dystopic sites of origin in the nasopharynx, in the maxillary sinuses, and intracranially have been reported (Seccia et al. 2010; Banerjee et al. 1992; Jugie et al. 1992; Sharma et al. 2002; Mariani et al. 2004; Wormald et al. 2011), a diagnosis of esthesioneuroblastoma outside the nasal cavity should only be made with great cautiousness (Mills 2002).

Symptoms are related to the site of origin and the local invasion and may present as long as several months prior to definite diagnosis (Dulguerov and Calcaterra 1992). Unilateral nasal obstruction, recurrent epistaxis, and – less common – anosmia are observed as well as ophthalmic manifestations like periorbital pain, excessive tearing, visual disturbance, or ptosis (Rakes et al. 1985). Occasionally headache, nerve palsies due to involvement of cranial nerves, or hormone excess syndromes such as Cushing syndrome or inappropriate antidiuretic hormone secretion have been reported (Osterman et al. 1986; Arnesen et al. 1994; Myers et al. 1994).

Table 18.1 Esthesioneuroblastoma: (modified) Kadish staging system and prognosis

Stage		Stage distribution	Disease-specific survival rates (at 10 years)	Stage distribution	Proposed therapy in children
		As reported in (Jethanamest et al. 2007) based on registry data, $n=261$, all ages		As reported in (Broich et al. 1997) based on systematic literature review, $n=553$, all ages	
A	Tumor confined to the nasal cavity	17.2%	90%	18.3%	Resection
B	Tumors involving the nasal cavity and extending into the paranasal sinuses	49.8%	68.3%	32.3%	Resection + radiotherapy
C	Tumor extending beyond the nasal cavity and paranasal sinuses (includes involvement of orbit, base of skull, intracranial cavity)	3.8%	66.7%	49.4%	Resection + radiotherapy ± (neoadjuvant) chemotherapy
D	Any tumor with distant sites	29.1%	35.6%		

In 1976, Kadish et al. (1976) proposed a staging system based on the pattern of spread (Table 18.1). Kadish A tumors are confined to the nasal cavity, while Kadish B tumors infiltrate the paranasal cavities. Kadish C tumors extend beyond the nasal and paranasal cavities (Kadish et al. 1976). Later, the system has been modified by adding the category Kadish D for tumors with metastases. The Kadish system correlates to prognosis and is still in use, although other systems based on the TMN classification have been proposed (Biller et al. 1990; Dulguerov and Calcaterra 1992). Larger cohorts report about one third of the patients to present with Kadish stage C.

Distant metastases are thought to be very rare and to occur in less than 10% of patients. Metastases to lung, CNS, bone, liver, and bone marrow have been reported (Franklin et al. 1987; Koka et al. 1998; Chao et al. 2001; Argiris et al. 2003; Bradley et al. 2003; Eich et al. 2003; Bachar et al. 2008). It is assumed that, due to the difficult diagnosis, parts of those reports include misdiagnosed tumors and that the real proportion of esthesioneuroblastoma with distant metastases is even lower, as reflected in more recent published series (Diaz et al. 2005). However, locoregional spread to cervical lymph nodes seems to be encountered more often. Approximately 5–10% of all patients present with evidence of disease in the neck, while cervical lymph node involvement in the course of the disease will be found up to a quarter of patients (Dulguerov et al. 2001; Rinaldo et al. 2002; Bachar et al. 2008; Gore and Zanation 2009; Ozsahin et al. 2010).

Investigations at initial work-up include CT scan which usually shows a homogenously enhancing lesion, with bone erosion, invasion of the adjacent structures, and often with calcifications. MRI images help to delineate the extent of the disease, which appear isointense or hypointense to brain on T1-weighted images and hyperintense on T2-weighted images with marked enhancement after gadolinium (reviewed in Thompson 2009) (Fig. 18.2).

Besides the imaging of the primary tumor site and the neck, the initial work-up should include the search for distant metastases in CNS, lung, liver, bone, and bone marrow. In bone marrow, multiple sites should be assessed as the diagnosis of neuroblastoma or rhabdomyosarcoma should be considered. Somatostatin receptor imaging and FDG-PET have been reported to give positive results in patients with esthesioneuroblastoma and might be helpful in assessing the extent of the disease at diagnosis and during treatment (Ramsay et al. 1996; Freeman et al. 2005; Nguyen et al. 2006; Rostomily et al. 2006). Only a single patient with esthesioneuroblastoma has been reported to show positive mIBG uptake (Kairemo et al. 1998), but mIBG scintigraphy might be helpful in those cases where a metastatic lesion of a neuroblastoma is discussed. However, these imaging techniques have not been systematically addressed in larger cohorts of patients with esthesioneuroblastoma so far.

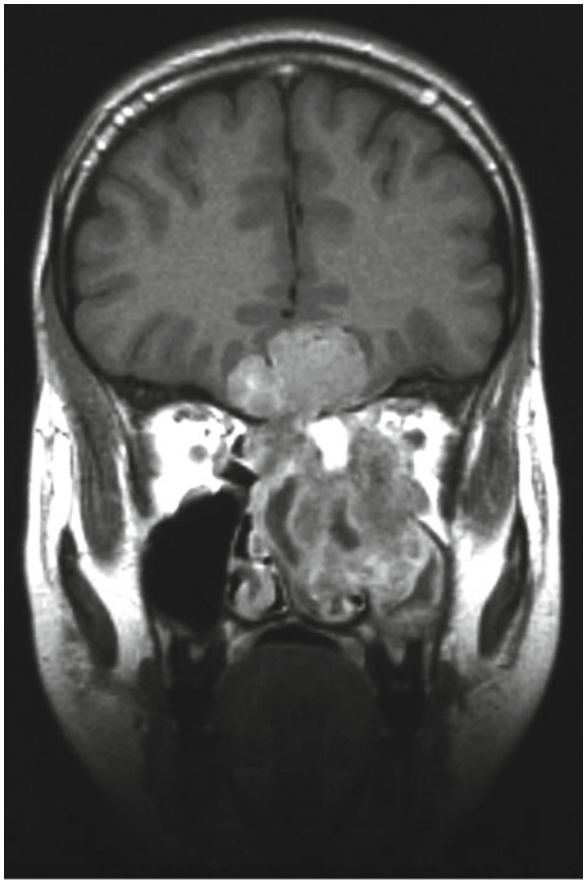

Fig. 18.2 Esthesioneuroblastoma, Kadish stage C, infiltrating the orbita, the nasal and paranasal cavities, and, through the lamina cribriformis, the brain (MRI)

18.3 Prognosis and Therapy

Due to the rareness of the disease, literature on prognosis is not reflected on large, homogenously treated cohorts. Nevertheless, it seems quite clear that grading, staging, the presence of metastases, and the treatment received influence prognosis. Kadish et al. reported patients with advanced stage (Kadish stage C) to be younger at diagnosis (median age 30.4 years) (Kadish et al. 1976). Vice versa, older age at diagnosis was correlated with better outcome in one series (<61 vs. >61 years) (Ozsahin et al. 2010), but this was not confirmed by others (<20 vs. >20 years (Eich et al. 2003); <50 vs. >50 years (Dulguerov and Calcaterra 1992)). In childhood, a high incidence of advanced stages is discussed (Lochrin 1989; Kumar et al. 2002), leading to the assumption that esthesioneuroblastoma in childhood shows an aggressive behavior; however this has never been proven in larger comparative studies.

To some extent, the amount of therapy needed is discussed controversially in the literature. Table 18.1 sets our proposal for the treatment in children in relation to the survival estimates as reported from a large cohort of 261 patients with esthesioneuroblastoma (Jethanamest et al. 2007).

Complete resection of the primary has been correlated to prognosis and is considered the backbone of all treatment strategies (Goldsweig and Sundaresan 1990; Devaiah and Andreoli 2009). Planning of the surgery may involve different subdisciplines (head and neck surgeons, neurosurgeons, ophthalmologists). Although most often open surgeries have been performed, endoscopic resections seem not to be inferior, as long as oncologic principles with clearance of margins are maintained (Lund et al. 2010; Snyderman et al. 2008; Folbe et al. 2009). To gain resectability in locally extended tumors, preoperative chemotherapy or radiotherapy proved efficient (Foote et al. 1993; Eich et al. 2003; Eich et al. 2005).

Kadish stage A tumors, especially when presenting with low-grade histology, seem to be sufficiently treated by surgery alone (with or without radiotherapy), but account only for a minor part of patients. In higher stages, the addition of radiotherapy with doses ranging from 55 to 65 Gy is claimed (Foote et al. 1993; Chao et al. 2001; Dulguerov et al. 2001; Eich et al. 2001). The planning of the radiotherapy may be hampered by adjacent endangered structures as eye and CNS and may require modern radiation techniques as intensity-modulated radiotherapy, proton irradiation, or stereotactic radiosurgery (Bhattacharyya et al. 1997; Walch et al. 2000; Zabel et al. 2002a, b; Tselis et al. 2008; Sterzing et al. 2009).

Although some authors abrogate the positive influence of chemotherapy, most authors support the need for a multimodal treatment strategy including surgery, radiotherapy, and chemotherapy in tumors of Kadish stage C (with or without metastases), however, without reaching a consensus on kind and amount of chemotherapy needed (Goldsweig and Sundaresan 1990; McElroy et al. 1998; Oskouian et al. 2002; Eich et al. 2003, 2005; Loy et al. 2006; McLean et al. 2007; Kiyota et al. 2008; Nichols et al. 2008; Porter et al. 2008). In children, chemotherapy regimen of soft tissue sarcoma or neuroblastoma protocols have often

been used; in adults, treatment with platinum-based regimens and others have been reported.

If cervical lymph nodes are involved, neck dissection and postoperative radiation therapy are discussed (Zanation et al. 2010), while cervical treatment seems not required in N0 patients. However, to discover late-evolving lymph nodes, adequate imaging of the neck should always be included in the follow-up of the patients (Gore and Zanation 2009).

Relapses and metastases usually develop within the first 2–3 years after diagnosis, but late relapses more than 5 years after therapy have been reported (Morita et al. 1993; Eden et al. 1994; Loy et al. 2006), indicating the need for a long follow-up, which, in a childhood population, should always include the care for therapy-related sequelae. The need for local control including expanded surgical procedures and high-dose radiotherapy poses specific problems in the pediatric age. Long-term sequelae in children include damage to craniofacial growth and permanent dentition, endocrine dysfunctions, and loss of sense of smell.

References

Argani P, Perez-Ordonez B et al (1998) Olfactory neuroblastoma is not related to the Ewing family of tumors: absence of EWS/FLI1 gene fusion and MIC2 expression. Am J Surg Pathol 22(4):391–398

Argiris A, Dutra J et al (2003) Esthesioneuroblastoma: the Northwestern University experience. Laryngoscope 113(1):155–160

Arnesen MA, Scheithauer BW et al (1994) Cushing's syndrome secondary to olfactory neuroblastoma. Ultrastruct Pathol 18(1–2):61–68

Bachar G, Goldstein DP et al (2008) Esthesioneuroblastoma: the Princess Margaret Hospital experience. Head Neck 30(12): 1607–1614

Banerjee AK, Sharma BS et al (1992) Intracranial olfactory neuroblastoma: evidence for olfactory epithelial origin. J Clin Pathol 45(4):299–302

Benoit MM, Bhattacharyya N et al (2008) Cancer of the nasal cavity in the pediatric population. Pediatrics 121(1):e141–e145

Bhattacharyya N, Thornton AF et al (1997) Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. Arch Otolaryngol Head Neck Surg 123(1):34–40

Biller HF, Lawson W et al (1990) Esthesioneuroblastoma: surgical treatment without radiation. Laryngoscope 100(11): 1199–1201

Bobele GB, Sexauer C et al (1994) Esthesioneuroblastoma presenting as an orbital mass in a young child. Med Pediatr Oncol 22(4):269–273

Bradley PJ, Jones NS et al (2003) Diagnosis and management of esthesioneuroblastoma. Curr Opin Otolaryngol Head Neck Surg 11(2):112–118

Broich G, Pagliari A et al (1997) Esthesioneuroblastoma: a general review of the cases published since the discovery of the tumour in 1924. Anticancer Res 17(4A):2683–2706

Chao KS, Kaplan C et al (2001) Esthesioneuroblastoma: the impact of treatment modality. Head Neck 23(9):749–757

Cohen ZR, Marmor E et al (2002) Misdiagnosis of olfactory neuroblastoma. Neurosurg Focus 12(5):e3

Devaiah AK, Andreoli MT (2009) Treatment of esthesioneuroblastoma: a 16-year meta-analysis of 361 patients. Laryngoscope 119(7):1412–1416

Diaz EM Jr, Johnigan RH 3rd et al (2005) Olfactory neuroblastoma: the 22-year experience at one comprehensive cancer center. Head Neck 27(2):138–149

Dulguerov P, Calcaterra T (1992) Esthesioneuroblastoma: the UCLA experience 1970–1990. Laryngoscope 102(8): 843–849

Dulguerov P, Allal AS et al (2001) Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol 2(11):683–690

Eden BV, Debo RF et al (1994) Esthesioneuroblastoma. Long-term outcome and patterns of failure–the University of Virginia experience. Cancer 73(10):2556–2562

Eich HT, Staar S et al (2001) Radiotherapy of esthesioneuroblastoma. Int J Radiat Oncol Biol Phys 49(1):155–160

Eich HT, Hero B et al (2003) Multimodality therapy including radiotherapy and chemotherapy improves event-free survival in stage C esthesioneuroblastoma. Strahlenther Onkol 179(4):233–240

Eich HT, Muller RP et al (2005) Esthesioneuroblastoma in childhood and adolescence. Better prognosis with multimodal treatment? Strahlenther Onkol 181(6):378–384

Elkon D, Hightower SI et al (1979) Esthesioneuroblastoma. Cancer 44(3):1087–1094

Faragalla H, Weinreb I (2009) Olfactory neuroblastoma: a review and update. Adv Anat Pathol 16(5):322–331

Ferlito A, Rinaldo A et al (2003) Contemporary clinical commentary: esthesioneuroblastoma: an update on management of the neck. Laryngoscope 113(11):1935–1938

Folbe A, Herzallah I et al (2009) Endoscopic endonasal resection of esthesioneuroblastoma: a multicenter study. Am J Rhinol Allergy 23(1):91–94

Foote RL, Morita A et al (1993) Esthesioneuroblastoma: the role of adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 27(4):835–842

Franklin D, Miller RH et al (1987) Esthesioneuroblastoma metastatic to the trachea. Head Neck Surg 10(2):102–106

Freeman SR, Mitra S et al (2005) Expression of somatostatin receptors in arginine vasopressin hormone-secreting olfactory neuroblastoma–report of two cases. Rhinology 43(1):61–65

Goldsweig HG, Sundaresan N (1990) Chemotherapy of recurrent esthesioneuroblastoma. Case report and review of the literature. Am J Clin Oncol 13(2):139–143

Gore MR, Zanation AM (2009) Salvage treatment of late neck metastasis in esthesioneuroblastoma: a meta-analysis. Arch Otolaryngol Head Neck Surg 135(10):1030–1034

Hirose T, Scheithauer BW et al (1995) Olfactory neuroblastoma. An immunohistochemical, ultrastructural, and flow cytometric study. Cancer 76(1):4–19

Hyams V, Batsakis JG, Michaels L, Armed Forces Institute of Pathology Fascicles (1988) Tumors of the upper respiratory tract and ear, vol 2. American Registry of Pathology Press, Washington D.C

Jethanamest D, Morris LG et al (2007) Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors. Arch Otolaryngol Head Neck Surg 133(3):276–280
Jugie M, Marsot-Dupuch K et al (1992) Unusual localization of an olfactory esthesioneuroma. Ann Radiol (Paris) 35(6): 477–482
Kadish S, Goodman M et al (1976) Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 37(3):1571–1576
Kairemo KJ, Jekunen AP et al (1998) Imaging of olfactory neuroblastoma–an analysis of 17 cases. Auris Nasus Larynx 25(2):173–179
Kiyota N, Tahara M et al (2008) Nonplatinum-based chemotherapy with irinotecan plus docetaxel for advanced or metastatic olfactory neuroblastoma: a retrospective analysis of 12 cases. Cancer 112(4):885–891
Koka VN, Julieron M et al (1998) Aesthesioneuroblastoma. J Laryngol Otol 112(7):628–633
Kumar M, Fallon RJ et al (2002) Esthesioneuroblastoma in children. J Pediatr Hematol Oncol 24(6):482–487
Lochrin C (1989) Esthesioneuroblastoma. Med Pediatr Oncol 17(5):433–438
Loy AH, Reibel JF et al (2006) Esthesioneuroblastoma: continued follow-up of a single institution's experience. Arch Otolaryngol Head Neck Surg 132(2):134–138
Lund VJ, Stammberger H, et al (2010) European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinol Suppl (22):1–143
Mariani L, Schaller B et al (2004) Esthesioneuroblastoma of the pituitary gland: a clinicopathological entity? Case report and review of the literature. J Neurosurg 101(6):1049–1052
McElroy EA Jr, Buckner JC et al (1998) Chemotherapy for advanced esthesioneuroblastoma: the Mayo Clinic experience. Neurosurgery 42(5):1023–1027, discussion 1027–1028
McLean JN, Nunley SR et al (2007) Combined modality therapy of esthesioneuroblastoma. Otolaryngol Head Neck Surg 136(6):998–1002
Mezzelani A, Tornielli S et al (1999) Esthesioneuroblastoma is not a member of the primitive peripheral neuroectodermal tumour-Ewing's group. Br J Cancer 81(4):586–591
Mills SE (2002) Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. Mod Pathol 15(3):264–278
Morita A, Ebersold MJ et al (1993) Esthesioneuroblastoma: prognosis and management. Neurosurgery 32(5):706–714, discussion 714–705
Myers SL, Hardy DA et al (1994) Olfactory neuroblastoma invading the oral cavity in a patient with inappropriate antidiuretic hormone secretion. Oral Surg Oral Med Oral Pathol 77(6):645–650
Nelson RS, Perlman EJ et al (1995) Is esthesioneuroblastoma a peripheral neuroectodermal tumor? Hum Pathol 26(6): 639–641
Nguyen BD, Roarke MC et al (2006) F-18 FDG PET/CT staging and posttherapeutic assessment of esthesioneuroblastoma. Clin Nucl Med 31(3):172–174
Nichols AC, Chan AW et al (2008) Esthesioneuroblastoma: the Massachusetts eye and ear infirmary and Massachusetts general hospital experience with craniofacial resection, proton beam radiation, and chemotherapy. Skull Base 18(5):327–337
Oskouian RJ Jr, Jane JA Sr et al (2002) Esthesioneuroblastoma: clinical presentation, radiological, and pathological features, treatment, review of the literature, and the University of Virginia experience. Neurosurg Focus 12(5):e4
Osterman J, Calhoun A et al (1986) Chronic syndrome of inappropriate antidiuretic hormone secretion and hypertension in a patient with olfactory neuroblastoma. Evidence of ectopic production of arginine vasopressin by the tumor. Arch Intern Med 146(9):1731–1735
Ozsahin M, Gruber G et al (2010) Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. Int J Radiat Oncol Biol Phys 78(4):992–997
Perkkio M, Majuri S et al (1991) A child with esthesioneuroblastoma with metastases to the spinal cord and the bone marrow. Med Pediatr Oncol 19(1):66–69
Porter AB, Bernold DM et al (2008) Retrospective review of adjuvant chemotherapy for esthesioneuroblastoma. J Neurooncol 90(2):201–204
Rakes SM, Yeatts RP et al (1985) Ophthalmic manifestations of esthesioneuroblastoma. Ophthalmology 92(12):1749–1753
Ramsay HA, Kairemo KJ et al (1996) Somatostatin receptor imaging of olfactory neuroblastoma. J Laryngol Otol 110(12): 1161–1163
Resto VA, Eisele DW et al (2000) Esthesioneuroblastoma: the Johns Hopkins experience. Head Neck 22(6):550–558
Rinaldo A, Ferlito A et al (2002) Esthesioneuroblastoma and cervical lymph node metastases: clinical and therapeutic implications. Acta Otolaryngol 122(2):215–221
Rostomily RC, Elias M et al (2006) Clinical utility of somatostatin receptor scintigraphic imaging (octreoscan) in esthesioneuroblastoma: a case study and survey of somatostatin receptor subtype expression. Head Neck 28(4):305–312
Seccia V, Lenzi R et al (2010) Ectopic olfactory neuroblastoma arising in the pterygopalatine fossa. Otolaryngol Head Neck Surg 142(3):460–461
Sharma SC, Reddy CE et al (2002) Isolated esthesioneuroblastoma of sphenoid sinus. Am J Otolaryngol 23(5):287–289
Snyderman CH, Carrau RL et al (2008) Endoscopic skull base surgery: principles of endonasal oncological surgery. J Surg Oncol 97(8):658–664
Sorensen PH, Wu JK et al (1996) Olfactory neuroblastoma is a peripheral primitive neuroectodermal tumor related to Ewing sarcoma. Proc Natl Acad Sci USA 93(3):1038–1043
Sterzing F, Stoiber EM et al (2009) Intensity Modulated Radiotherapy (IMRT) in the treatment of children and adolescents–a single institution's experience and a review of the literature. Radiat Oncol 4:37
Thompson LD (2009) Olfactory neuroblastoma. Head Neck Pathol 3(3):252–259
Tselis N, Heyd R et al (2008) Interstitial high-dose-rate-brachytherapy in advanced esthesioneuroblastoma. Laryngoscope 118(11): 2006–2010
Walch C, Stammberger H et al (2000) The minimally invasive approach to olfactory neuroblastoma: combined endoscopic and stereotactic treatment. Laryngoscope 110(4): 635–640
Woerner SJ, Lazerson J et al (1986) Olfactory neuroblastoma (esthesioneuroblastoma) in a 2-year-old boy. Pediatr Hematol Oncol 3(2):167–174

Wormald R, Lennon P et al (2011) Ectopic olfactory neuroblastoma: report of four cases and a review of the literature. Eur Arch Otorhinolaryngol 268(4):555–560

Zabel A, Thilmann C et al (2002a) The role of stereotactically guided conformal radiotherapy for local tumor control of esthesioneuroblastoma. Strahlenther Onkol 178(4):187–191

Zabel A, Thilmann C et al (2002b) Comparison of forward planned conformal radiation therapy and inverse planned intensity modulated radiation therapy for esthesioneuroblastoma. Br J Radiol 75(892):356–361

Zanation AM, Ferlito A et al (2010) When, how and why to treat the neck in patients with esthesioneuroblastoma: a review. Eur Arch Otorhinolaryngol 267(11):1667–1671

Germ Cell Tumors of the Head and Neck

19

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19.1 Introduction

The general aspects of germ cell tumors, common to all tumors, occurring at different sites, are discussed in the introduction chapter of germ cell tumors and genitourinary cancers (Chap. 39). Germ cell tumors of the head and neck region constitute rare, but characteristic extragonadal germ cell tumors of childhood (Jordan and Gauderer 1988). They most commonly present in the neonatal period or during infancy (Bernbeck et al. 2009). In this age group, virtually all tumors are mature or immature teratomas. A significant proportion of tumors are already diagnosed during prenatal ultrasound (Berge et al. 2004; Dunn et al. 1992).

In the perspective of the overall favorable prognosis, the diagnosis of a large, mostly cystic cervical tumor must not evoke therapeutic nihilism and lead to the recommendation of termination of pregnancy, but should rather lead to a close follow-up during pregnancy and optimal planning of the perinatal management (Langer et al. 1992; Backer et al. 2004; Bernbeck et al. 2009; Kerner et al. 1998).

Some tumors may include malignant yolk sac tumor components, sometimes only as microscopic foci. The risk of clinically relevant malignant yolk sac tumor components that are also associated with significant AFP secretion rises with age. Thus, among the rare head and neck germ cell tumors diagnosed beyond the first year of life, the majority show malignant yolk sac tumor as leading histology (Bernbeck et al. 2009). Other histologic subtypes of germ cell tumors only rarely develop at this site, and to the authors' knowledge, no seminoma has yet been reported in the head and neck region. No genetic survey of these tumors has been reported so far. Rare single reports indicate for

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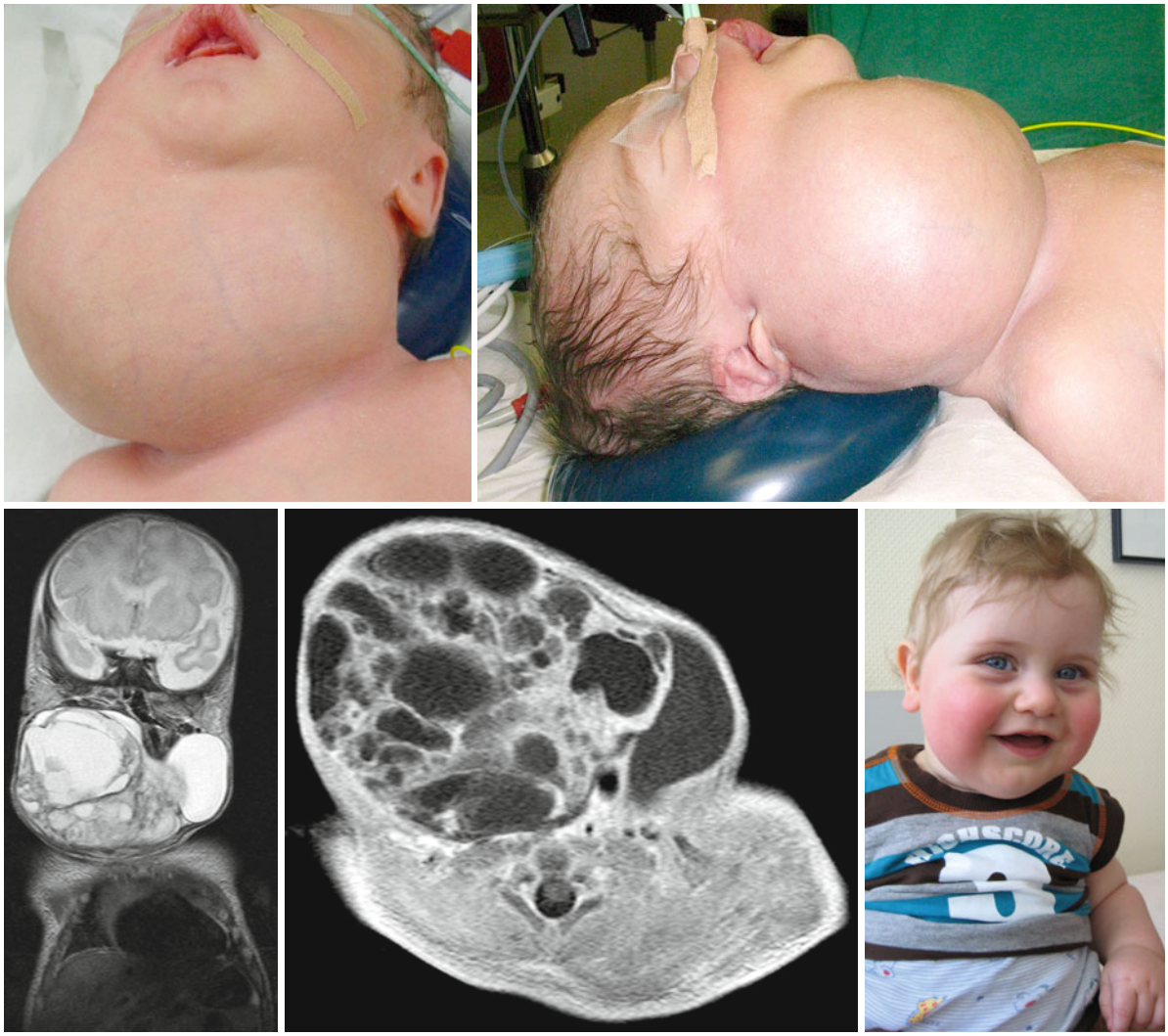

Fig. 19.1 Clinical images and magnetic resonance imaging of a neonate with a huge mature cervical teratoma involving the thyroids. The tumor was diagnosed with prenatal ultrasound. The patient was delivered with cesarean section and immediately intubated and ventilated after birth. At the second day of life, the tumor was completely resected including the thyroid gland which presented as the presumed site of tumor origin. After surgery, the patient showed intercurrent palsy of the vocal cords and hypocalcemia. Both resolved within weeks. The patient is on support of thyroid hormones. The boy is nicely developing without signs of neurocognitive deficits. (The pictures are kindly provided by Dr. M. Albrecht and Dr. Schmitz-Stolbrink, Westphalian Children's Centre, Dortmund)

genetic aberrations characteristic of germ cell tumors of infancy and childhood.

19.2 Clinical Diagnosis

Most tumors are diagnosed during the perinatal period. In countries which promote prenatal ultrasound assessment of the fetus, the majority of tumors are diagnosed with fetal ultrasound (Dunn et al. 1992). Tumors, in particular teratomas, present as partially solid and cystic lesions in the head and neck region, often in close association to the pharynx (Fig. 19.1). Vascular malformations and tumors such as lymphangioma constitute the most problematic differential diagnosis. Fetal MRI may assist in assessing the nature of the tumor and in evaluating the organ of origin of the tumor. Some tumors may develop within or in close anatomical proximity to the

thyroid gland. If a head and neck tumor is diagnosed prenatally, a close follow-up schedule is mandatory in order to compare the growth kinetics of the tumor and the fetus, respectively. In addition, significant hemodynamic distress caused by increased blood flow through the tumor should be excluded. These parameters may assist in planning of the time of delivery.

At birth, head and neck teratomas commonly present as large tumors, covered by skin. Due to airway compression, neonates may have asphyxia, and severe respiratory distress may occur. In these patients, primary tracheal intubation and ventilatory support are mandatory.

During infancy and childhood, head and neck germ cell tumors present as circumscribed tumors, mostly arising in the pharyngeal region or the nasal sinuses. The majority of tumors are malignant yolk sac tumors. Nevertheless, metastases rarely occur and mostly involve the cervical lymph nodes or the lungs.

In order to exclude malignant yolk sac tumor or choriocarcinoma, the measurement of AFP and β-HCG is recommended (Table 19.1). AFP levels must be compared to the age-related reference values (Blohm et al. 1998). In addition, the general considerations with regard to the diagnostic impact of tumor markers in germ cell tumors also apply to the head and neck germ cell tumors (see Chap. 39).

Prior to surgery, clinical assessment should include an endocrinologic work-up, specifically focusing on the thyroid and parathyroid function.

19.3 Therapy

In contrast to other teratomas and malignant germ cell tumors, the prognosis of head and neck germ cell tumors is primarily determined by the optimal management of local complications, which are primarily related to airway obstruction. Therefore, despite their benign histology, teratomas of the head and neck region constitute a life-threatening and potentially fatal disease. In a situation of suboptimal perinatal care, asphyxia may result in life-long neurological impairment. Therefore, careful planning of the perinatal management is absolutely mandatory, and treatment should be reserved to experienced neonatologic and pediatric surgical teams.

In the most comprehensive reviews by Jordan and Gauderer in 1988 and by Kerner et al. in 1998, a decrease in mortality from 37% to 25% has been described (Kerner et al. 1998; Jordan and Gauderer 1988). In most instances, patients died during the neonatal period as a result of respiratory failure caused by external airway obstruction. Different measures have been supposed to reduce perinatal risk, including intrapartum airway management (ex utero and intrapartum (EXIT) maneuver) or access to the airway in utero prior to delivery (Liechty et al. 1997; Hullett et al. 2006; Backer et al. 2004). However, the combined data of more-recent publications still report a high mortality in 5 of 16 cases (Martino et al. 2006) (Table 19.1).

In conclusion, optimal pre- and perinatal management is essential for successful management of head and neck germ cell tumors. The recommended clinical approach to prenatally detected teratomas includes repeated ultrasound, allowing for an optimized timing of delivery. Rapid tumor growth in utero may then necessitate a premature elective cesarean section. It is apparent that children with suspected large head and neck germ cell tumors should be referred to tertiary care centers that may provide optimal interdisciplinary management, including experienced neonatologists, pediatric anesthesiologists, pediatric oncologists, ear and nose and pediatric surgeons. Infants should be delivered through cesarean section, and in case of respiratory distress, immediate laryngotracheal intubation is required. To our knowledge cricotomy is required infrequently.

In a recent series reported from the German MAKEI study group, none of the patients received an ante- or intrapartum airway advice. Nevertheless, no newborn died perinatally, and significant asphyxia could also be avoided (Bernbeck et al. 2009). In 12 patients, repeated ultrasounds in short intervals demonstrated a marked enlargement of the tumor within a few days leading to preterm delivery during the 32nd to 37th week of pregnancy. Of note, the growth velocity after delivery was unpredictable. Six tumors showed dramatic tumor growth immediately after birth, while in others the growth velocity declined. As a consequence, three neonates were operated on soon after birth in an emergency situation. In tumors showing rapid growth, no beneficial short-time effects of chemotherapy have been reported, substantiating the central importance of timely planning and performance of tumor resection.

Notably, the tumor site has a significant impact on the therapeutic approach. Teratomas of the neck are usually better assessable to complete resection than pharyngeal tumors, in which microscopically complete tumor resection is often impossible (Bernbeck et al. 2009).

Table 19.1 Specific diagnostic strategy in head and neck tumors, suspicious of germ cell tumors

Procedure	Specific questions
Clinical assessment	
Physical examination	Signs of upper airway obstruction
Laboratory assessment	
AFP (β-HCG)	Malignant germ cell tumor with yolk sac tumor – consider age-related reference range (or choriocarcinoma)
Catecholamines	Exclusion of neuroblastoma
Thyroid hormones	Hypothyroidism – pre- and postsurgery
Calcium, phosphate	Hypoparathyroidism – pre- and postsurgery
Radiographic assessment	
Prenatal ultrasound	Site, organ of origin, cystic structures or calcification, observation of growth kinetics, timing of delivery
Head and neck MRI (+ angiography)	Site, size, organ of origin, cystic structures, calcification, involvement of larynx, pharynx, thyroid gland, proximity to large vessels and airways
Abdominal ultrasound	Liver metastases (if elevated AFP/YST)
Lung X-ray	Lung metastases (if elevated AFP/YST)
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)
(β-HCG)	Exclusion of choriocarcinoma
(CD-30)	Exclusion of embryonal carcinoma
(OCT3/4)	Exclusion of seminoma (embryonal carcinoma)

In the latter patients, it might be helpful to postpone surgery until the infant's weight has significantly increased in order to facilitate complete resection. However this is only possible if tumor size and growth velocity do not argue against a further delay. Moreover, a delayed tumor resection may bear the potential risk of malignant overgrowth. In this context, it should be noted that tumors of newborns may already include some small foci of yolk sac tumor. It should be considered that in teratomas of different sites in particular at the sacrococcygeal region, YST may be the leading histology at relapse. Therefore, preoperative chemotherapy aiming for the elimination of potential YST microfoci may be considered in selected patients with unresectable tumors in whom delayed tumor resection is reasonable. Nevertheless, these patients presumably constitute absolutely rare exceptions from the general rule that surgery is the mainstay of treatment.

During infancy, the risk of malignant germ cell tumors increases with age but may vary according to tumor site (Schneider et al. 2004). In a large series of teratomas registered to the German MAKEI studies, all children older than 1 year suffered from malignant germ cell tumors with yolk sac tumor as the leading histology (Göbel et al. 1998). This observation supports the meta-analysis of Kerner et al. that included children with malignant cervical germ cell tumors (Kerner et al. 1998). However, the biological switch from histologically benign teratomas to mixed malignant germ cell tumors with yolk sac tumor elements remains to be elucidated for this specific tumor site. In sacrococcygeal germ cell tumors, which contribute about 40% of all germ cell tumors in pediatric registries, the risk for malignant overgrowth rises after the second month of life. Prior to the age of 2 months, the incidence of malignant germ cell tumors was 10% in males and 7% in females, whereas at 6 months two thirds of the boys and about half of the girls had malignant tumors. In contrast, all germ cell tumors of the vagina registered in the MAKEI registry occurred in early childhood (<2 years), and the exclusive histology was yolk sac tumor (Mauz-Körholz et al. 2000). Again, these site-specific patterns illustrate the varying malignant potential of germ cell tumors depending on age, sex and primary site.

19.4 Prognosis

With a multidisciplinary approach, patients with germ cell tumors of the head and neck region have a favorable chance of survival and cure from their tumors.

The optimal perinatal and neonatal management, in particular postnatal life support in case of airway obstruction, strongly determines long-term outcome and presumably also neurological outcome if neonatal hypoxia can be avoided.

The oncologic prognosis is then determined by surgical experience and the ability to completely remove the tumor. Nevertheless, even with optimal management, patients may still suffer from late sequelae. These are predominantly related to local complications caused by the tumor or surgical therapy. Therefore, one important future issue will be to evaluate in how far early maybe even prenatal interventions or a centralization of the treatment to both neonatologic and pediatric oncologic centers will help to reduce or even avoid some of these handicaps.

References

Berge SJ, von Lindern JJ, Appel T, Braumann B, Niederhagen B (2004) Diagnosis and management of cervical teratomas. Br J Oral Maxillofac Surg 42:41–45

Bernbeck B, Schneider DT, Bernbeck B, Koch S, Teske C, Lentrodt J, Harms D, Göbel U, Calaminus G (2009) Germ cell tumors of the head and neck: report from the MAKEI Study Group. Pediatr Blood Cancer 52:223–226

Blohm ME, Vesterling-Hörner D, Calaminus G, Göbel U (1998) Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol 15:135–142

De Backer A, Madern GC, van de Ven CP, Tibboel D, Hazebroek FW (2004) Strategy for management of newborns with cervical teratoma. J Perinat Med 32:500–508

Dunn CJ, Nguyen DL, Leonard JC (1992) Ultrasound diagnosis of immature cervical teratoma: a case report. Am J Perinatol 9:445–447

Göbel U, Calaminus G, Engert J, Kaatsch P, Gadner H, Bökkerink JP, Hass RJ, Waag K, Blohm ME, Dippert S, Teske C, Harms D (1998) Teratomas in infancy and childhood. Med Pediatr Oncol 31:8–15

Hullett BJ, Shine NP, Chambers NA (2006) Airway management of three cases of congenital cervical teratoma. Paediatr Anaesth 16:794–798

Jordan RB, Gauderer MW (1988) Cervical teratomas: an analysis. Literature review and proposed classification. J Pediatr Surg 23:583–591

Kerner B, Flaum E, Mathews H, Carlson DE, Pepkowitz SH, Hixon H, Graham JM Jr (1998) Cervical teratoma: prenatal diagnosis and long-term follow-up. Prenat Diagn 18: 51–59

Langer JC, Tabb T, Thompson P, Paes BA, Caco CC (1992) Management of prenatally diagnosed tracheal obstruction: access to the airway in utero prior to delivery. Fetal Diagn Ther 7:12–16

Liechty KW, Crombleholme TM, Flake AW, Morgan MA, Kurth CD, Hubbard AM, Adzick NS (1997) Intrapartum airway management for giant fetal neck masses: the EXIT (ex utero intrapartum treatment) procedure. Am J Obstet Gynecol 177:870–874

Martino F, Avila LF, Encinas JL, Luis AL, Olivares P, Lassaletta L, Nistal M, Tovar JA (2006) Teratomas of the neck and mediastinum in children. Pediatr Surg Int 22:627–634

Mauz-Körholz C, Harms D, Calaminus G, Göbel U (2000) Primary chemotherapy and conservative surgery for vaginal yolk-sac tumour. Maligne Keimzelltumoren Study Group. Lancet 355:625

Schneider DT, Calaminus G, Koch S, Teske C, Schmidt P, Haas RJ, Harms D, Göbel U (2004) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42: 169–175

Odontogenic Tumors

20

Jan Godzinski, Roberto Bianchi, and Marco Guzzo

Contents

Odontogenic tumors (OT) derive from epithelial, ectomesenchymal, and or mesenchymal elements that still are or have been part of the tooth-forming apparatus. Therefore, they are found exclusively within the maxillofacial skeleton or in the soft tissue overlying tooth-bearing areas. These tumors are classified according to WHO histological classification published in 2005 (Barnes et al. 2005). There are few reports on OT in children (Adebayo et al. 2002; Asamoa et al. 1990; Guerrisi et al. 2007; Ulmansky et al. 1999). The literature shows these neoplasms accounted for between 1.0 and 28.8% of the oral lesion (Ulmansky et al. 1999).

Comparative studies of OT in children are difficult because various authors use differing classifications; age groups and patients are of different racial origins. Basically, all the defined histotypes can occur in children although most of them and particularly the malignant counterpart are rare in such patients.

The most common OT in children are reported in Table 20.1 and Table 20.2. There appears to be a racial predilection for OT types.

20.1 Ameloblastoma

Ameloblastoma, or adamantinoma as this tumor was named before 1930, is a rare benign tumor originating from odontogenic epithelium with mature, fibrous stroma without odontogenic ectomesenchyma. It is one of the most frequent OT in all age group, but the peak incidence is in the third–forth decades. About 10–15% of them occurred in children. According to WHO classification, four types have been described as follows: a solid/multicystic (about 70% of all), an

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Table 20.1 Odontogenic tumors in children and adolescent. Review of the literature

Authors	No. of cases	Geographic area	Histotype	%
Adebajo et al. (2002)	78	Nigeria	Ameloblastoma	54
			Myxoma	19
			Adenomatoid odontogenic tumor	9
			Ameloblastic fibroma	8
			Odontoma	9
			Others	
Guerrisi et al. (2007)	153	Argentina	Odontoma	50
			Ameloblastoma	18.3
			Myxoma	8.5
			Adenomatoid odontogenic tumor	5.2
			Others	
Jones and Franklin (2006)	243	United Kingdom	Odontoma	79.4
			Adenomatoid odontogenic tumor	4
			Ameloblastoma	3.7
			Ameloblastic fibroma	3.3
			Others	
Ulmansky et al. (1999)	18	Israel	Myxoma	38.8
			Ameloblastic fibroma	22.2
			Ameloblastic fibro-odontoma	22.2
			Ameloblastoma	11
			Others	
Sato et al. (1997)	79	Japan	Odontoma	59.5
			Ameloblastoma	34
			Others	

Table 20.2 Diagnostic workflow of odontogenic tumors

Physical examination	In most benign tumors, signs and symptoms are scarce. Sometimes slow swelling of jaw and/or movement of teeth can be noted. Less frequently can occur as painless exophytic-like lesion of the alveolar mucosa. In contrast, pain is the most frequent symptoms followed by rapid swelling of the bone in malignant odontogenic tumors
Laboratory assessment	None
Radiological assessment	
– First assessment	More often discovered incidentally during the course of routine intraoral dental (plain) radiographs or panoramic radiography
– Preoperative assessment	Panoramic radiography, CT
– FU	Panoramic radiography
Pathological assessment	Most odontogenic tumors are benign, and the diagnosis can be only achieved by clinical and radiological evaluations. Histological confirmation is often necessary and should be always obtained before planning a nonconservative surgery
Staging system (odontogenic carcinomas)	Usually, it is not applied
Grading system (odontogenic carcinomas)	Malignant odontogenic tumors are exceedingly rare in children and are usually highly aggressive. Grading is still definited by histotype
General treatment guidelines	Need for multidisciplinary approach Need for referral to center with expert physicians professionally dedicated to the management of this neoplasms in adults (or strict collaboration with them)
– Surgery	Keystone of treatment. Complete segmental bone resection, enucleation or curettage according to histotypes. Immediate bone graft is recommended in order to prevent facial deformity
– Radiotherapy	High-grade tumors are very rare
– Chemotherapy	Palliative intent

extraosseous/peripheral (1.3–10% of all), a desmoplastic (rare), and a unicystic (5–15% of all) type (Barnes et al. 2005). Some studies reported that the unicystic type is the most common type in children (Ord et al. 2002), but the relevant literature shows the rate of solid type is higher than unicystic type (Zhang et al. 2010). Solid and unicystic types locate usually in the mandible (more than 90% of the cases). While the mandible-to-maxilla ratio is 1:1 and 2.4:1 for desmoplastic and extraosseous type, respectively. In the mandible, the tumor has a marked predilection for the posterior region except in African Blacks in whom the tumor occurs in the symphysis (Chidzonga 1996). Localizations in other bones are described but very rarely (Kessler and Dominiquez 1986). Solid/multicystic, unicystic, and desmoplastic ameloblastoma grow slowly but may markedly deform involved portions of the bone. Diagnosis based on clinical appearance may reveal swelling of the corresponding area of face and mandible or maxillary intraosseous mass. Pain or paresthesia is rare. Solid/multicystic types may be diagnosed as unilocular or multilocular (soap bubble-like) radiolucencies at panograph X-ray or CT scan. An unerupted tooth may be associated. The roots of the involved tooth may be eroded. Despite characteristic imaging, microscopic confirmation of diagnosis is recommended. Unicystic type radiographically present as a unilocular, often pericoronal radiolucency, that may also be associated with an unerupted tooth. Desmoplastic ameloblastoma shows a pronounced stromal component compressing the odontogenic epithelial component. Consequently, about 50% of them are radiographically present as a mottled, mixed radiolucency/radiopacity with ill-defined borders. Extraosseous ameloblastoma usually is located to the alveolar mucosa in edentulous area. This tumor grows as an exophytic-like lesion determining a superficial erosion of the bone crest due to pressure resorption (Stevenson and Austin 1990) (Figs. 20.1–20.7).

Once the diagnosis is established, the treatment may be planned. Surgery is the treatment of choice. In children, the decision for treatment strategy should be made according to the patient's age, tumor size, location, and whether it is a primary or a recurring tumor. Resection usually creates fewer difficulties than reconstruction of the mandible. Although ameloblastoma is not a malignant disease, surgeons must keep in mind that complete excision of this locally aggressive tumor is the mainstay of treatment. Enucleation or curettage leads to risk of

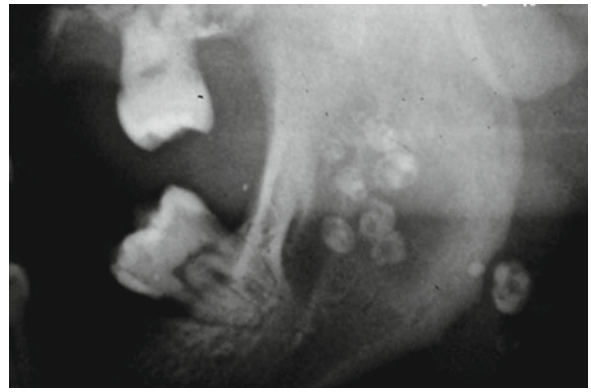

Fig. 20.1 Odontoma compound type in an 18-year-old girl

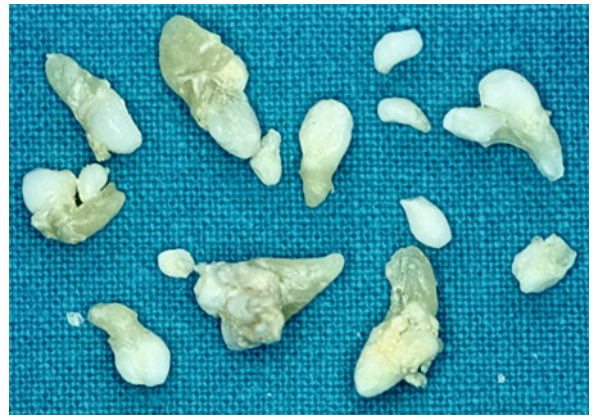

Fig. 20.2 Macroscopic specimen of odontoma compound type in an 18-year-old girl

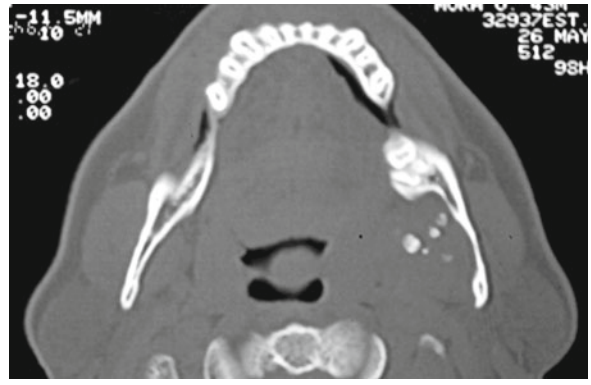

Fig. 20.3 Computed tomography of odontoma compound type in an 18-year-old girl

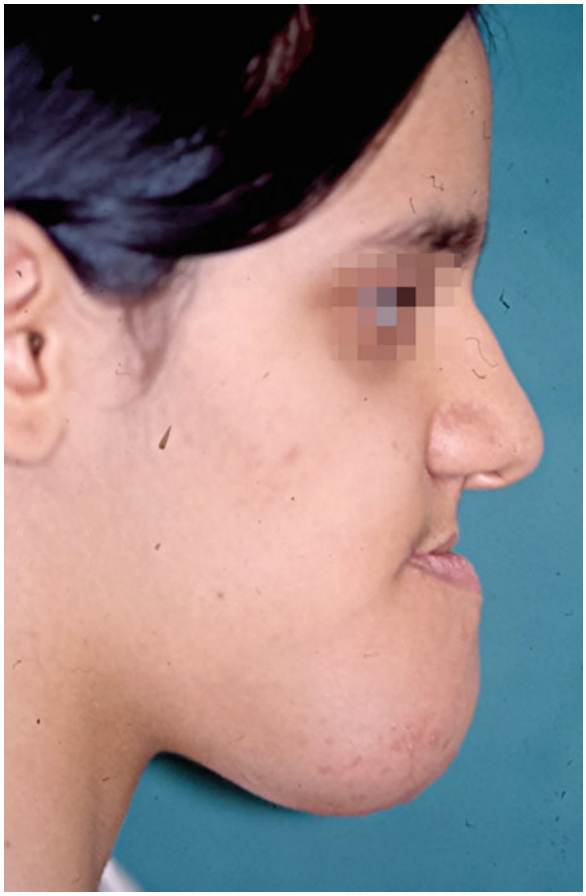

Fig. 20.4 Cementoblastoma in a 17-year-old girl

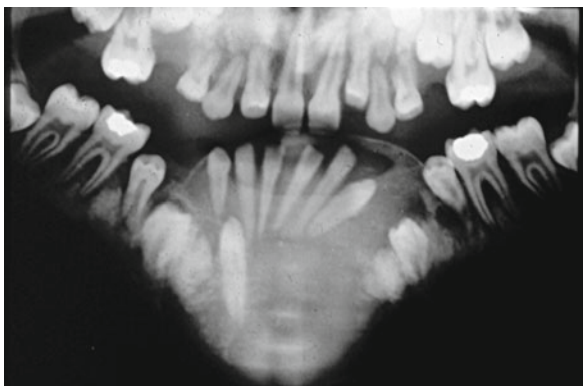

Fig. 20.5 Ortho-panoramic X-ray of cementoblastoma in a 17-year-old girl

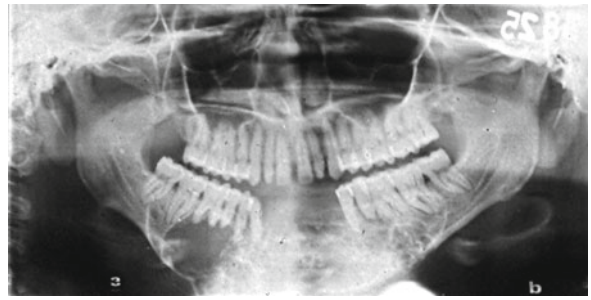

Fig. 20.6 Ortho-panoramic X-ray of ameloblastoma of the mandible extending from 4.7 to 3.7

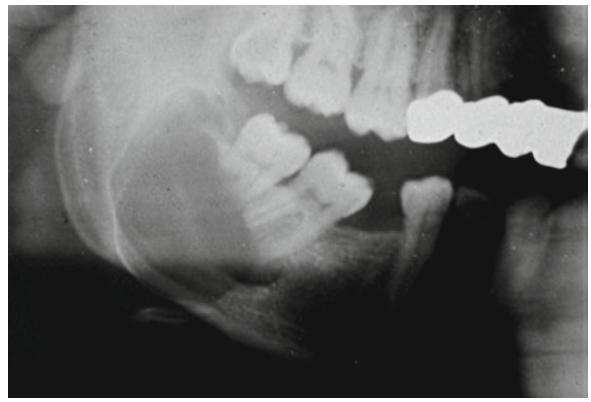

Fig. 20.7 Ortho-panoramic X-ray of ameloblastoma of the right mandible. Unilocular radiolucency resembling cysts with scalloped borders

recurrence as high as 25–40%. The block resection of the tumor with subsequent reconstruction with bone graft is routinely recommended. In more advanced cases, the segmental resection of mandible followed by complete reconstruction may be necessary. Biopsy for histological confirmation is often necessary and should be always obtained before planning a nonconservative surgery (Zhang et al. 2010). Unicystic ameloblastoma is thought to recur less frequently than other subtypes, thus some authors advocate also less aggressive treatment in this form of tumor and reserve more aggressive surgery for any recurrence. However, a recent large review revealed that this histotype is aggressive and should be treated as solid ameloblastoma (Philipsen and Reichart 1998).

The tumor usually recurs in between 1 and 15 years of follow-up with a peak within 5 years from surgery (Ord et al. 2002). Consequently, a long-term postoperative follow-up seems reasonable.

The complementary treatments, as chemotherapy or radiotherapy, are of limited value. In spite of a benign histologic aspect, some ameloblastoma may spread distant metastases, mainly to the lungs (metastasizing ameloblastoma). Moreover, an ameloblastic

carcinoma may arise from a benign ameloblasoma either intraosseous or peripheral (Barnes et al. 2005).

References

Adebayo ET, Ajike SO, Adekeye EO (2002) Odontogenic tumours in children and adolescents: a study of 78 Nigerian cases. J Craniomaxillofac Surg 30(5):267–272

Asamoa EA, Ayanlere AO, Olaitan AA, Adekeye EO (1990) Paediatric tumours of the jaws in northern Nigeria. Clinical presentation and treatment. J Craniomaxillofac Surg 18(3):130–135

Barnes L, Eveson JW, Reichart P, Sidransky D (2005) Pathology and genetics of head and neck tumours. IARC Press, Lyon

Chidzonga MM (1996) Ameloblastoma in children. The Zimbabwean experience. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81(2):168–170

Guerrisi M, Piloni MJ, Keszler A (2007) Odontogenic tumors in children and adolescents. A 15-year retrospective study in Argentina. Med Oral Patol Oral Cir Bucal 12(3):E180–E185

Jones AV, Franklin CD (2006) An analysis of oral and maxillofacial pathology found in children over a 30-year period. Int J Paediatr Dent 16(1):19–30

Kessler A, Dominiquez FZ (1986) Ameloblastoma in childhood. J Oral Maxillofac Surg 44:609–611, Ref Type: Generic

Ord RA, Blanchaert RH Jr, Nikitakis NG, Sauk JJ (2002) Ameloblastoma in children. J Oral Maxillofac Surg 60(7):762–770

Philipsen HP, Reichart PA (1998) Unicystic ameloblastoma. A review of 193 cases from the literature. Oral Oncol 34(5):317–325

Sato M, Tanaka N, Sato T, Amagasa T (1997) Oral and maxillofacial tumours in children: a review. Br J Oral Maxillofac Surg 35(2):92–95

Stevenson AR, Austin BW (1990) A case of ameloblastoma presenting as an exophytic gingival lesion. J Periodontol 61(6):378–381

Ulmansky M, Lustmann J, Balkin N (1999) Tumors and tumor-like lesions of the oral cavity and related structures in Israeli children. Int J Oral Maxillofac Surg 28(4):291–294

Zhang J, Gu Z, Jiang L, Zhao J, Tian M, Zhou J et al (2010) Ameloblastoma in children and adolescents. Br J Oral Maxillofac Surg 48(7):549–554

Salivary Gland Tumors

21

Marco Guzzo and Jan Godzinski

Contents

21.1 Introduction

Inflammatory tumors and benign cysts represent the major cause of salivary gland enlargements in children. In case of a tumor, hemangioma is the most common histotype within the salivary glands in these patients (Baker and Malone 1985; Lack and Upton 1988). The high percentage of vascular tumors reported by many authors exceeds the number of cases registered with the Armed Force Institute of Pathology (AFIP). In fact, the large experience of the AFIP reports benign mesenchymal tumors occurring in only 12.3% (8.1% hemangiomas) of all cases of salivary gland tumors under the age of 17 years, while 42.5% of these cases are benign and 42.9% are malignant epithelial tumors (Ellis et al. 1991).

21.2 Differential Diagnosis and Management of Rare Head and Neck Tumors

21.2.1 Hemangioma

Hemangiomas usually evolve in three clinical phases: they may rapidly enlarge to reach their largest size over a period of 6–8 months. Then, after a second period of 22–24 months, they begin a last period of regression.

The adequate diagnosis is usually possible on the basis of clinical appearance and noninvasive diagnostic techniques. Open biopsy can be often avoided since ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI) are reported to give an accurate picture of the disease.

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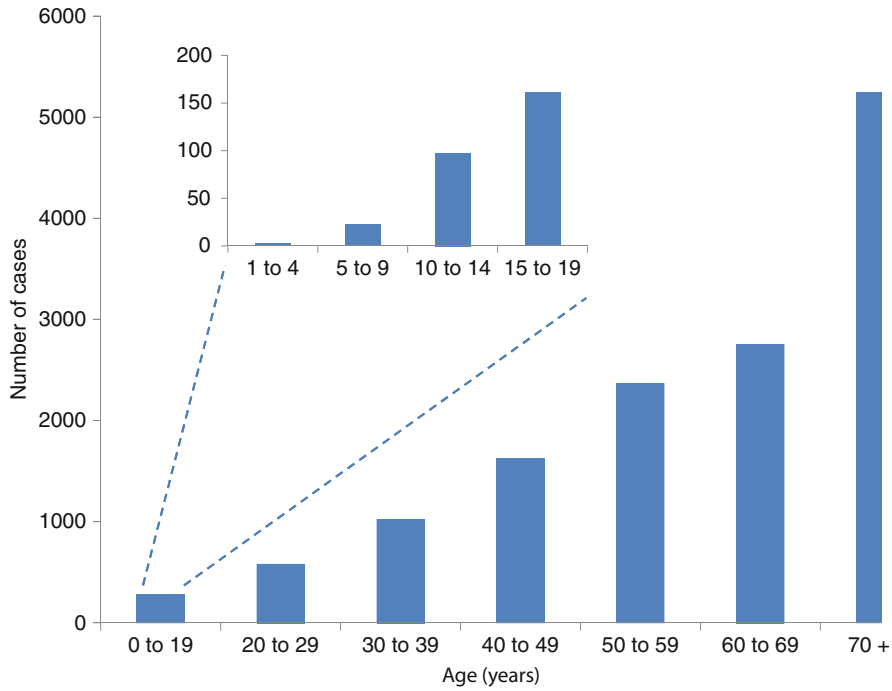

Fig. 21.1 Age distribution of patients with salivary gland tumors in the SEER 17 database (1973–2007). The window shows the age distribution of children/adolescents. (Courtesy of Dr. Iyad Sultan, King Hussein Cancer Center, Amman, Jordan)

Management of hemangioma varies from surgical excision and/or systemic treatment with propranolol to wait-and-see policy expecting spontaneous regressions. Many authors recommend avoiding futile surgical removal of hemangioma from infant patient until after the patient has reached school age. In fact, it has been estimated that up to 80% of hemangioma in infants involute by the age of 7 years. Thus, no more than 20% of them need surgical treatment. Surgery should be only considered if medical therapy will be ineffective and for aesthetical purpose after medical treatment.

Since propranolol was introduced to the treatment of hemangioma in 2008 (Leute-Labreze et al. 2008), steroids, interferon, and, to some extent, laser therapy have limited applications. Propranolol has been reported as the most promising drug for the treatment of hemangioma in infancy, even if, to date, there has not been any definitive study on optimal dose range, safety, and side effects. The treatment is generally well tolerated; however, the side effect profile can include hypersomnolence, reflux, bronchospasm, hypotension hypoglycemia, and, rarely, failure to thrive. Although no relevant cardiac and hemodynamic changes were noted during β-blocker treatment, a safety protocol before starting the therapy, including cardiac ultrasonography and cardiac examination, is mandatory (Buckmiller 2009; Leboulanger et al. 2010; Schiestl et al. 2010). Radiation therapy is a historical method (Bhandarwar et al. 2008). The question of the optimal therapeutic strategy is still widely discussed.

21.2.2 Epithelial Salivary Gland Neoplasms

Epithelial salivary gland neoplasms are infrequent both in adults and children, accounting for <3% of all head and neck tumors. About 5% of them occur in patients <18 years of age (Fig. 21.1). Compared to adults, a slight female preponderance and a higher occurrence in black children/adolescents were observed. Such neoplasms are usually divided into benign (pleomorphic adenoma, Warthin's tumor, basal cell adenoma, oncocytoma, myoepithelioma, and cystadenoma) and malignant (mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, adenocarcinoma NOS, carcinoma ex pleomorphic adenoma, squamous cell carcinoma, clear cell carcinoma, small cell carcinoma, and carcinosarcoma) tumors (Ellis 1991) (Fig. 21.2). The major salivary glands are the main site of occurrence, being the parotid affected in about 80% of the cases (see Table 21.1). In children, malignant tumors accounted for about 50% of cases as compared

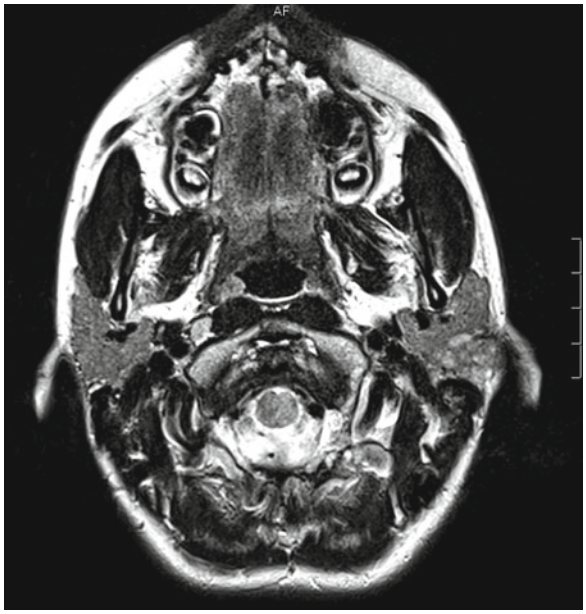

Fig. 21.2 Mucoepidermoid carcinoma in a 15-year-old girl

to 37% reported by the adult literature. Also different in children is the distribution of benign and malignant histotypes among the salivary gland. Malignant tumors affected the parotid gland in about 50% of published pediatric series, while in the submandibular gland, benign neoplasms were twice as frequent as malignant tumors. In adults, malignant tumors comprised 25–32% of tumors of the parotid gland and 40–50% of submandibular gland neoplasms (Table 21.2). Among benign tumors, pleomorphic adenomas account for more than 70% of pediatric cases, and mucoepidermoid carcinomas represent about 50% of malignant cases, followed by acinic cell carcinomas (34.6%) and adenoid cystic carcinomas (5.3%) (Sultan et al. 2010).

It is of interest that in young patients, malignant tumors have been diagnosed as low–intermediate grade in about 87% of the cases (<50% in adults).

Leading symptom of epithelial salivary gland neoplasms is usually painless swelling within the parotid or – less frequently – the submandibular gland. Imaging includes ultrasound and MRI (CT) to define local-regional extension of the disease. Fine-needle aspiration biopsy may be helpful in pretreatment confirmation of the nature of the disease but is strongly suggested in the case of submandibular swelling since tumors are very rare in that region.

Surgery is the mainstay of treatment for both benign and malignant tumors. Parotidectomy (superficial or total) seems to be the best approach for achieving surgical resection of the neoplasms with clear margins. Since the tumors usually arise in the superficial glandular lobe, the formal identification and dissection of the facial nerve followed by the

Table 21.1 Epithelial salivary gland tumors in children. Review of series reported in the English literature. Distribution by site and histology

Authors	No. cases	Parotid		Submandibular gland		Others	
		Benign tumors	Malignant tumors	Benign tumors	Malignant tumors	Benign tumors	Malignant tumors
Lack and Upton (1988)	25	5	13	4	–	1	2
Callender et al. (1992)	29	6	18	1	3	1	
De Cassia Braga Ribeiro et al. (2002)	38	4	20	5	2	2	5
Shikhani and Johns (1988)	21	14	2	4	1		
Baker and Malone (1985)	13	–	12	–	1		
Fonseca et al. (1991)	24	12	6	3		2	1
Rogers et al. (1994)	8	–	7	–	1		
Orvidas et al. (2000)	43	27	16	ND	ND	ND	ND
Ethunandan et al. (2003)	12	9	3	ND	ND	ND	ND
Kessler and Handler (1994)	15	6	6	1	2		
Guzzo et al. (2006)	52	32	9	4	1	1	5
Total	280	115	112	22	11	7	13
Parotid	227 (81%)	51%	49%				
Submandibular gland	33 (12%)			67%	33%		
Others	20 (7%)						

ND no data, parotid tumors only

Table 21.2 Salivary gland malignant tumors grading system

- Tumors in which grading is still defined by histotype:
  - Low-grade carcinoma:
    - Acinic cell carcinoma
    - Basel cell carcinoma
    - Polymorphous low-grade adenocarcinoma
  - High-grade carcinoma:
    - Salivary duct carcinoma
    - Squamous cell carcinoma
    - Undifferentiated carcinoma
- Tumors in which specific grading system is applied:
  - Adenocarcinoma, NOS:
    - Grading according to the cytologic variability
  - Adenoid cystic carcinoma:
    - Intermediate vs. high grade, depending on histologic patterns
  - Mucoepidermoid carcinoma:
    - Low vs. intermediate vs. high grade, depending on five histopathologic features
  - Carcinoma ex pleomorphic adenoma:
    - Grading correlated with histologic subtype of the carcinoma component

resection of the suprafacial portion of the gland (superficial parotidectomy) represent the safest approach both for nerve preservation and oncological purpose. In young patients, postoperative facial nerve injury is a critical risk in parotid surgery compared with adults. Tumor resection or limited excision of the parotid and submandibular gland is discouraged because of high risk of incomplete tumor removal. Moreover, high risk of nerve damage should be expected when the operation is performed without the formal identification of the facial nerve.

For benign tumors, local relapses after limited resection and superficial parotidectomy are reported to be 39% and 19%, respectively. For malignant tumors, local recurrences were seen in 48% and 31% of the cases after limited or standard surgery, respectively (Shikhani and Johns 1988). About 90% of the young patients with malignant tumors are diagnosed as clinically N0 (70% in adults), and occult metastases in the neck are rare. Consequently, simultaneous neck dissection is recommended only when neck metastases are detectable.

The role of radiotherapy in salivary gland tumors remains controversial (Guzzo et al. 2006; Sessions et al. 1993). The presence of high-grade malignancies, a large and aggressive tumor mass, involvement of multiple levels of cervical lymph nodes and microscopically incomplete resection are considered the main indications for irradiation. However, in children – given the higher risk of postirradiation complications, such as facial growth retardation, dental anomalies, and second malignant neoplasms – radiotherapy is usually recommended in highly selected cases only.

There are limited clinical data to help define the role of systemic therapy in the palliative management of salivary gland cancer. Conventional cytotoxic regimens include cyclophosphamide, Adriamycin, cisplatinum, (CAP), and 5-fluorouracil (FACP) combinations. The role of paclitaxel in the treatment of adenoid cystic carcinomas (ACC) is still controversially discussed – possibly being effective in selected cases (Gilber et al. 2006; Till and Martins 2008).

Clinical trials – with the goal to evaluate the possible efficacy of imatinib mesylate in patients with cancers expressing c-kit, of cetuximab (Erbitux) – a monoclonal antibody that binds to the epidermal growth factor receptor – and of antiandrogen drugs in salivary duct carcinoma expressing androgen receptors are still ongoing (Fan et al. 2001; Laurie and Licitra 2006).

Malignant epithelial tumors of the salivary gland in children usually have a good prognosis. The five-year overall survival ranges from 81% to 90%, reaching 100% in some series (Guzzo et al. 2006). The general good prognosis in children is probably due to the more favorable clinical presentation; however, whether age-related differences in biology exist remains unclear (Sultan et al. 2010). It is recommended that children and adolescents with salivary gland tumors are referred to specialized centers, preferably in which cooperation between pediatric oncologist, ENT surgeon, and adult experts may optimize the chances for young patients to be cured with limited morbidity (Table 21.3).

21.2.3 Very Rare Entities

Two very rare conditions shall also be mentioned. The first is sialoblastoma – a rare congenital low-grade malignant tumor with a resemblance to fetal salivary tissue. The parotid gland is affected in more than 75% of the cases. This neoplasm requires surgical treatment. Recurrences are common. The role of chemotherapy and radiotherapy remain to be clarified (Dalal et al. 2009; Ellis and Auclair 2008). Another one is a tumor-like condition which can occur in HIV-infected patients. Parotid gland or sometimes submandibular gland swelling may be the first clinical manifestation

Table 21.3 A general view: practical diagnostic and therapeutic guidelines for salivary glands tumors

Physical examination	Signs and symptoms: painless glandular swelling. Parotid gland and, less frequently, submandibular gland. Rarely in the minor salivary gland of the soft and hard palate Anamnesis: an average duration of the symptoms of 12 months Children >10 years of age
Laboratory assessment	Exclude infection, acute inflammation, and lymphoma
Radiological assessment	
– First assessment	Ultrasonography
– Preop assessment	Magnetic resonance
Pathological assessment	FNAB mandatory Delay surgery when inflammatory tumors or cysts are suspected
Staging system (carcinomas of the mayor salivary glands)	*TNM UICC AJCC 2009 (seventh ed.)* T1: tumor 2 cm or less in greatest dimension without extraparenchymal extension* T2: tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension* T3: tumor more than 4 cm and/or tumor with extraparenchymal extension* T4a: tumor invades skin, mandible, ear canal, and/or facial nerve T4b: tumor invades base of skull and /or pterygoid plates and/or encase carotid artery Nx: regional lymph node metastasis cannot be assessed N0: no regional lymph node metastasis N1: metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension N2: metastasis as described below: – N2a: metastasis in a single ipsilateral lymph node, 3–6 cm – N2b: metastasis in multiple ipsilateral lymph nodes, <6 cm – N2c: metastasis in bilateral or contralateral lymph nodes, <6 cm N3: metastasis in lymph node >6 cm M0: no distant metastasis M1: distant metastasis
Stage grouping	Stage I: T1 N0 M0 Stage II: T2 N0 M0 Stage III: T3 N0 M0; T1, T2, T3 N1 M0 Stage IVA: T4a, T4b N0 N1 M0; T1, T2, T3, T4a N2 M0 Stage IVB: T4b any N M0; any T N3 M0 Stage VIC: any T, any N M1
General treatment guidelines	Need for multidisciplinary approach Need for referral to prime oncology center with expert physicians professionally dedicated to the management of this cancer in adults (or strict collaboration with them)
– Surgery	Keystone of treatment Parotidectomy (superficial or total) is the best approach on primary Neck dissection is recommended only when neck metastases are clinically detected
– Radiotherapy	Recommended limiting radiation in selected patients (high-grade tumors very rare)
– Chemotherapy	No role

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissue or nerve, except those listed under T4a and 4b. Microscopic evidence alone does not constitute Extraparenchymal extension for classificative purposes

of HIV infection. Most of these enlargements are probably acute infections, but either lymphoid hyperplasia or lymphoepithelial cysts and lymphoepithelial lesions (salivary diffuse infiltrative lymphocytosis syndrome) can be associated. Salivary gland swelling is usually bilateral and accompanied by cervical lymph node enlargement. Medical treatment with antiviral drugs has been reported to be effective in controlling parotid swelling. Surgery and radiation therapy have also been used (Sessions et al. 1993; Ellis and Auclair 2008).

References

Baker SR, Malone B (1985) Salivary gland malignancies in children. Cancer 55:1730–1736

Bhandarwar AH et al (2008) A rare case report of parotid haemangioma in a child treated by sclerotherapy using bleomycin. Bombay Hospital Journal 50(4):672–675

Buckmiller LM (2009) Propranolol for infantile hemangiomas. Curr Opin Otolaryngol Head Neck Surg 17:458–459

Callender DL et al (1992) Salivary gland neoplasms in children. Arch Otolaryngol Head Neck Surg 118:472–476

Dalal S et al (2009) Sialoblastoma: a rare pediatric tumour of the salivary glands. Internet J Surg 2(2)

De Cassia Braga Ribeiro K et al (2002) Epithelial salivary glands neoplasms in children and adolescent: a forty-four-year experience. Med Pediatr Oncol 39:594–600

Ellis GL, Auclair PL (2008) Tumors of the salivary glands. AFIP, Washington

Ellis GL et al (1991) Armed Force Institute of Pathology (AFIP) surgical pathology of the salivary glands. W.B. Saunders Company, Philadelphia

Ethunandan M et al (2003) Parotid neoplasms in children: experience of diagnosis and management in a district general hospital. Int J Oral Maxillofac Surg 32:373–377

Fan CY et al (2001) Expression of androgen receptor, epidermal growth factor receptor and transforming growth α in salivary duct carcinoma. Arch Otolaryngol Head Neck Surg 127:1075–1079

Fonseca I et al (1991) Epithelial salivary gland tumors of children and adolescents in southern Portugal. Oral Surg Oral Med Oral Pathol 72:696–701

Gilber J et al (2006) Phase II trial of taxol in salivary gland malignancies: a trial of the Eastern Cooperative Group. Head Neck 28:197–204

Guzzo M et al (2006) Salivary gland neoplasms in children: the experience of the Istituto Nazionale Tumori of Milan. Pediatr Blood Cancer 47(6):806–810

International Union Against Cancer (UICC) (2009) TNM classification of malignant tumors. 7th edn. Wiley-Blackwell

Kessler A, Handler SD (1994) Salivary gland neoplasms in children: a 10-year survey at the Children's Hospital of Philadelphia. Int J Pediatr Otorhinolaryngol 29:195–202

Lack EE, Upton MP (1988) Histopathologic review of salivary gland tumors in childhood. Arch Otolaryngol Head Neck Surg 114:898–906

Laurie SA, Licitra L (2006) Systemic therapy in the palliative management of advanced salivary gland cancers. J Clin Oncol 24:2673–2678

Leboulanger N et al (2010) Propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma: a preliminary retrospective study of French experience. Int J Pediatr Otorhinolaryngol 74:1254–1257

Leute-Labreze C et al (2008) Propranolol for severe haemangiomas of infancy. N Engl J Med 358(24):2649–2651

Orvidas LJ et al (2000) Pediatric parotid masses. Arch Otolaryngol Head Neck Surg 126:177–184

Rogers DA et al (1994) Primary malignancy of the salivary gland in children. J Pediatr Surg 26:44–47

Schiestl C et al (2010) Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas. Eur J Pediatr 170(4):493–501, Published online Oct 2010

Sessions RB et al (1993) Tumors of the salivary glands and paragangliomas. In: DeVitta V, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology. JB Lippincott, Philadelphia

Shikhani AH, Johns ME (1988) Tumors of the major salivary glands in children. Head Neck 10:257–263

Sultan I et al. (2010) Salivary gland carcinomas in children and adolescents population-based study, with comparison to adult cases. Head Neck. 2011 Oct;33(10):1476–1481

Till BG, Martins RG (2008) Response to paclitaxel in adenoid cystic carcinoma of the salivary gland. Head Neck 30:810–814

Laryngeal Tumors

22

Roberto Bianchi, Jan Godzinski, and Marco Guzzo

Content

Laryngeal tumors are extremely rare in children and adolescent, thus extensive experience with laryngeal neoplasms under the age of 18 years is very limited, even in major head and neck cancer centers. Dyspnoea, dysphonia, hoarseness, and dysphagia are symptoms which shall lead to a suspicion of laryngeal mass: in these cases flexible fiberoptic laryngoscopic examination is mandatory. Any suspicious case must be scheduled for a direct microlaryngoscopy and biopsy under general anesthesia, which allows for both establishing the local relationships and taking a sample for microscopic examination (Kato et al. 1991; Sessions et al. 1993; Strong and Jako 1972). Diagnosis is frequently delayed, due to the rarity of this disease, but early detection of any malignancy located in this critical region is of greatest value, so any persistent change in a child's voice or hoarseness is an indication for prompt and adequate diagnostic work-up in order to treat the disease with a conservative approach, avoiding mutilative surgery.

The clinical extension of the neoplasm must be precisely assessed. Computed tomography and MRI are useful for local–regional assessment. Distant metastasis must be searched mainly in the lungs, bones, and liver and, in case of rhabdomyosarcoma, also in bone marrow (Pransky and Kang 2003).

Among benign neoplasms, the most common is *subglottic hemangioma*: it behaves like other hemangioma of the head and neck (see salivary gland tumors chapter for further details) with the possible additional complication of airway obstruction and/or dysphagia in the proliferative phase of a wide lesion. Subglottic hemangioma occurs in a 2:1 female to male ratio and prefers the left posterior-lateral subglottic mucosa. Diagnosis is made at a mean age of 3.6 months (Bitar et al. 2005).

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Infants with subglottic hemangioma and cutaneous facial hemangiomas in a "beard" distribution should be evaluated for PHACE syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, and Eye abnormalities) (Smith et al. 2004).

The optimal treatment of subglottic hemangioma is still not defined: a wait-and-see policy, based on spontaneous regression of the lesion, is indicated in asymptomatic cases without respiratory distress, while transoral laser resection is the most common approach for small and circumscribed lesions, with a success rate of 88.9% using a mean of two sessions. Intralesional corticosteroids injection has been used with a success rate of 86.4%, using a mean of three injections; unfortunately, it requires general anesthesia and postoperative intubation (Bitar et al. 2005).

Tracheotomy is advised to secure airway in case of extensive hemangioma. Open-neck surgical excision was performed in the past, but is reserved to cases resistant to all conservative treatments today.

Systemic treatment includes corticosteroids, alpha-interferon and, since 2008, propranolol, which is taught to displace other drugs in the medical cure of pediatric hemangiomas.

Other benign submucosal lesions include the *nerve sheath tumors*: 10% of them are diagnosed in patients under the age of 21 years, and 25–40% of such lesions occur in the head and neck region. They derive from the Schwann cell of peripheral nerves and include neurilemmoma, which is a solitary encapsulated tumor that very rarely shows malignant change, and neurofibroma, a non-encapsulated neoplasm that can be found in multiple locations (when associated with von Recklinghausen's disease) and can undergo malignant degeneration in 10% of cases, usually into malignant peripheral nerve sheet tumor (MPNST), rarely into liposarcomas (Pulli and Coniglio 1997; Golledge et al. 1995).

The vast majority of laryngeal nerve sheath tumors are supraglottic, with the aryepiglottic fold and false vocal cord being the most common sites. They are not radio-sensitive, and thus transoral laser excision is the treatment of choice (Pulli and Coniglio 1997).

Granular cell tumors are uncommon neoplasms that appear most frequently in the tongue; in pediatric population laryngeal involvement is very rare and usually subglottical. These tumors are usually benign, with slow growth; the treatment is based on a surgical approach, usually complete removal with carbon dioxide laser (Holland et al. 1998).

Table 22.1 Summary of two reviews of malignant tumors of the larynx in children by Gindhart and Ferlito. (Ferlito et al. 1999; Ginhart et al. 1980)

Histotype	Gindhart et al. (1980) No. of patients (%)	Ferlito et al. (1999) No. of patients (%)
Rhabdomyosarcoma		20 (42.5)
Squamous cell carcinoma	53 (98.2)	13 (27.6)
Synovial sarcoma		3 (6.4)
Malignant fibrous histiocytoma		2 (4.3)
Non-Hodgkin's lymphoma		2 (4.3)
Chondrosarcoma		1
Ewing sarcoma		1
Fibrosarcoma		1
Malignant schwannoma		1
Mixed sarcoma		1
Mucoepidermoid carcinoma		1
Adenocarcinoma	1	
Primitive neuroectodermal tumor		1
Total	54 (100)	47 (100)

Inflammatory myofibroblastic tumor is an uncommon neoplasm that is usually located in the lung in pediatric population; it rarely occurs in the larynx and in this site it does not appear so aggressive as in other locations. This tumor is usually indolent, does not metastasize and can rarely recur locally. The mainstay of treatment is wide local excision (Rodrigues et al. 2005).

Hamarthoma of the larynx is very rare; Rinaldo and colleagues reviewed 11 cases from the literature and 5 of them occurred in children. Treatment consists of local excision; recurrences are usually seen associated with incomplete removal (Rinaldo et al. 1998).

Malignant tumors of the larynx are rare in children. Two of the most extensive and recent reviews are reported by Gindhart and Ferlito in Table 22.1 (Ferlito et al. 1999; Ginhart et al. 1980).

Rhabdomyosarcoma is the most common sarcoma arising in the larynx and the average age of the patients at the diagnosis is 9 years and 2 months (Ferlito et al. 1999). Sarcomas have well-established strategies of treatment (see chapter 44).

The local treatment in case of laryngeal location, however, remains challenging. Radical resections are clearly mutilating, conservative surgery may not be

complete and radiotherapy is followed by well-known postirradiation complications. A limited series of laryngeal rhabdomyosarcomas from Institut Gustave Roussy, published in 1991, underlines the rarity of this location (5 cases among 126 patients with rhabdomyosarcoma treated in that center from 1955 to 1981) and a very good survival, achieved with chemotherapy and radiotherapy, avoiding mutilative surgery (no laryngectomies in this series). Authors also emphasize on long-term important sequelae associated with radiotherapy, such as arrest in growth of irradiated structures, huskiness, subclinical thyroid insufficiency, abnormalities in offspring, carotid stenosis, and an increased risk of radiation-induced malignancy (Ferlito et al. 1999; Kato et al. 1991; Nikaghlagh et al. 2007).

Other malignant mesenchymal tumors located in the larynx are also reported, but taking into account the variety of the histological subtypes, the incidence of each is negligible.

Squamous cell carcinoma (SCC) is the second most frequent pediatric malignancy of the larynx. However, some authors consider this tumor more frequent than rhabdomyosarcoma (Ferlito et al. 1999; Ginhart et al. 1980; Pransky and Kang 2003; Smith 2008). Etiology is controversial and it is not related to the well-recognized risk factors for laryngeal cancer in adults: pediatric SCC of the larynx seems to be a genetic disease in which there is an interaction between environmental, genetic, and immunological factors, such as:

- Malignant spontaneous degeneration of juvenile papilloma of the larynx (Figs. 22.1 and 22.2)
- Previous radiation therapy for a benign condition, such as adenoid hypertrophy
- Asbestos exposure
- Second-hand smoke
- Presence of chromosomal translocation (15;19)
- Infection with Human Papilloma Virus (Chow et al. 2007; Ferlito et al. 1999; Joos et al. 2009)

Recent studies have suggested that the prognosis of laryngeal SCC may be affected by the presence of chromosomal translocation (15;19) or human papilloma virus (HPV) DNA.

Several authors evaluated the role of chromosomal translocation (15;19) in young patients with carcinoma of the upper aerodigestive tract and found that the balanced chromosomal translocation t(15;19), resulting in the *BRD4-NUT* fusion oncogene, is part of a distinct clinicopathological entity characterized by young age, female predilection, midline epithelial carcinoma of the neck or upper thorax (as far as we concern, larynx),

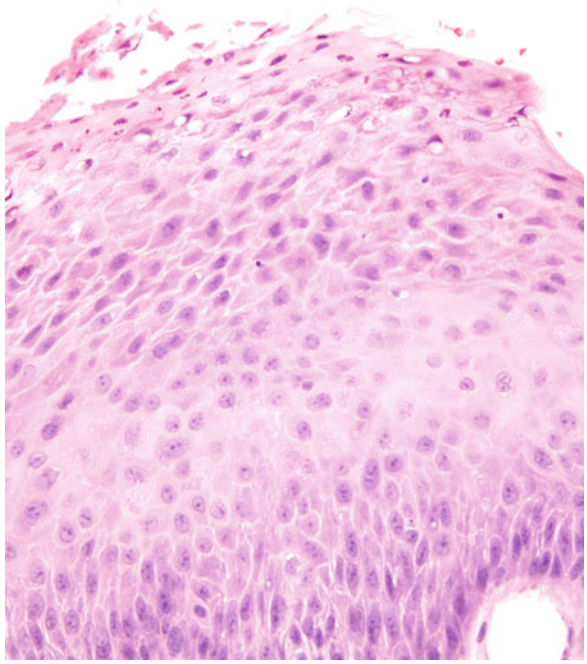

Fig. 22.1 Laryngeal papillomatosis

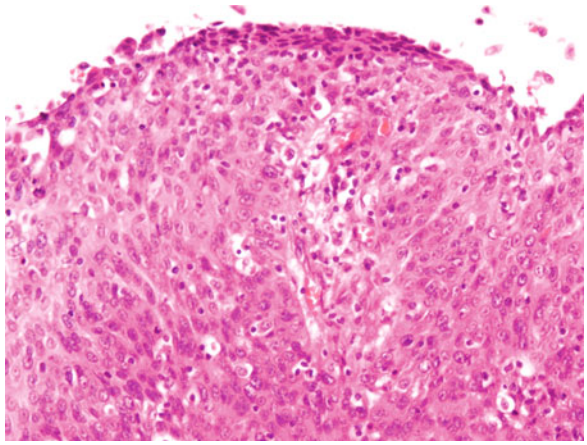

Fig. 22.2 Laryngeal papillomatosis in transformation to carcinoma

and a very poor prognosis, despite aggressive multimodal treatment (Vargas et al. 2001; Rahbar et al. 2003; French et al. 2004).

Most studies show a HPV positivity rate in head–neck SCC close to 35%; with regard to SCC of the larynx, the frequency of HPV positivity varies from 13% to 50% and the most frequently isolated subtype is HPV-16 (Chow et al. 2007; Joos et al. 2009). In the literature there are sporadic cases of SCC of the larynx in children that are positive for HPV DNA, but the real

Table 22.2 Management of laryngeal squamous cell carcinoma in children and adolescents

	Anamnesis: prolonged and worsening symptoms, diagnosis is frequently delayed, due to the rarity of this disease. The average age is 12 and 9 years for SCC and sarcomas, respectively
Physical examination	Signs and symptoms: persistent dysphonia or hoarseness, eventually associated with dyspnea and dysphagia; rarely cervical painless lymphadenopathy. Flexible fiberoptic laryngoscopic examination is mandatory. Any suspicious case must be scheduled for a direct microlaryngoscopy and biopsy. Vocal folds are the most common site of involvement by SCC (Squamous Cell Carcinoma) in adolescent
	Anamnesis: prolonged and worsening symptoms, diagnosis is frequently delayed, due to the rarity of this disease. The average age is 12 and 9 years for SCC and sarcomas, respectively
Laboratory assessment	There are no specific alterations
Radiological assessment	
– First assessment	MRI or CT of the neck
– Pretreatment assessment	Metastatic work-up includes CT/PET
– FU	MRI or CT, CT/PET periodically
Pathological assessment	Biopsy during direct microlaryngoscopy under general anesthesia, consider tracheotomy in advanced/stenosing neoplasm, before any other treatment
Staging system (carcinomas of the larynx)	TNM UICC AJCC (seventh ed.)
	The larynx is divided into three sites (supraglottis, glottis, and subglottis) and several subsites
	Supraglottis (suprahyoid epiglottis, aryepiglottic fold, arytenoid, infrahyoid epiglottis, and ventricular bands or false cords)
	Tis: carcinoma in situ
	T1: tumor limited to one subsite of supraglottis with normal vocal cord mobility
	T2: tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., base of tongue, vallecula, and medial wall of piriform sinus) without fixation of the larynx
	T3: tumor limited to larynx with vocal cord fixation, and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
	T4a: tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of the neck including deep/extrinsic muscle of tongue, strap muscles, thyroid, and esophagus
	T4b: tumor invades prevertebral space, encases carotid artery or mediastinal structures
	Glottis (vocal cords, anterior commissure, and posterior commissure)
	Tis: carcinoma in situ
	T1: tumor limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
	T1a tumor limited to one vocal cord
	T1b tumor involves both vocal cords
	T2: tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
	T3: tumor limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or inner cortex of the thyroid cartilage
	T4a: tumor invades through the outer cortex of the thyroid cartilage, and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscles of tongue, strap muscles, thyroid, and esophagus
	T4b: tumor invades prevertebral space and encases carotid artery or mediastinal structures
	Subglottis
	Tis: carcinoma in situ
	T1: tumor limited to subglottis
	T2: tumor extends to vocal cord(s) with normal or impaired mobility
	T3: tumor limited to larynx with vocal cord fixation
	T4a: tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the
	larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscles of tongue, strap muscles, thyroid, and esophagus
	T4b: tumor invades prevertebral space, encases carotid artery or mediastinal structures
	Nx: regional lymph node metastasis cannot be assessed

Table 22.2 (continued)

	Anamnesis: prolonged and worsening symptoms, diagnosis is frequently delayed, due to the rarity of this disease. The average age is 12 and 9 years for SCC and sarcomas, respectively
	N0: no regional lymph node metastasis N1: metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension N2: metastasis as described below: –N2a metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension –N2b metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension –N2c metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension N3: metastasis in lymph node more than 6 cm in greatest dimension M0: no distant metastasis M1: distant metastasis
Stage grouping	Stage 0: Tis N0 M0 Stage I: T1 N0 M0 Stage II: T2 N0 M0 Stage III: T1,T2 N1 M0; T3 N0,N1 M0 Stage IVA: T4a,T4b N0,N1 M0; T1,T2,T3, N2 M0 Stage IVB: T4b any N M0; Any T, N3 M0 Stage VIC: any T, Any N M1
General treatment guidelines	–Need for multidisciplinary approach –Need for referral to prime oncology center with expert physicians professionally dedicated to the management of this cancer in adults (or strict collaboration with them) because pediatric treatment protocols have not been well established due to the scarcity of cases; are based upon stage of the tumor
– Surgery	Conservative technique (open-neck or laser transoral surgery) are recommended when feasible; total laryngectomy is reserved in case of relapse
– Radiotherapy	Radical in early-stage disease and in sarcomas, after neoadjuvant chemotherapy; adjuvant with or without chemotherapy in high-risk patients after surgery; concomitant with chemotherapy in organ-preservation techniques. Consider long-term complications (arrest in growth of irradiated structures and radiation-induced malignancy)
– Chemotherapy	Neoadjuvant in advanced stages; concomitant with radiotherapy in organ-preservation strategies or in postoperative treatment of high-risk patients

pathogenetic role of HPV infection is still under debate. However, it seems that this virus has not any implication in the genesis of laryngeal cancer, in contrast with oropharynx (Joos et al. 2009; Simon et al. 1994)

In children, the average age for SCC of the larynx is 12 years, and 60% of cases affect boys, compared to adults, in whom there is a greater male predominance (Ferlito et al. 1999; Joos et al. 2009). Vocal folds are the most common site of origin followed by supraglottic and subglottic locations (Joos et al. 2009).

SCC of the children has been reported to mirror that of adults, in regard to the pattern of local spread and is usually well differentiated and keratinizing (Joos et al. 2009). This characteristic potentially offers good chance for survival, and reasonable efforts to spare good laryngeal function must be undertaken. On the other hand, some reports emphasize a poorer outcome between 15 and 19 years of age (60.1% 5-year survival) than in those aged over 20 (87.7% 5-year survival) (Rutt et al. 2010). Radiotherapy and surgery are the treatment of choice and, depending on tumor extension, may be used alone or in combination (Kato et al. 1991; Pransky and Kang 2003; Preuss et al. 2009; Sessions et al. 1993; Strong and Jako 1972). Small lesions may be managed successfully with laser surgery, and by using this method only very limited sequelae were seen (Ambrosch 2007; Pransky and Kang 2003; Strong and Jako 1972; McWother and Hoffman 2005). Chemotherapy potentially applies to advanced stage laryngeal cancers and shall probably be based on the experience gained in adults (Holsinger et al. 2009; Strong and Jako 1972).

In summary, the management of children with laryngeal carcinoma (Table 22.2) remains a challenge: early diagnosis of children presenting with symptoms

suggestive of laryngeal pathology is essential in order to secure definitive local therapy and minimize long-term complications.

A malignant hemopathy such as *non-Hodgkin's lymphoma* or, rarely, an *extramedullary plasmacytoma* could affect the larynx. In these cases, histologic examination of the biopsy specimen is fundamental to address cures that are based on chemotherapy and radiotherapy (Ferlito et al. 1999; Rutherford et al. 2009).

References

Ambrosch P (2007) The role of the laser microsurgery in the treatment of laryngeal cancer. Curr Opin Otolaryngol Head Neck Surg 2(15):82–88

Bitar MA et al (2005) Management of congenital subglottic hemangioma: trends and success over the past 17 year. Otolaryngol Head Neck Surg 132:226–231

Chow CW et al (2007) Squamous cell carcinomas in children and young adults: a new wave of a very rare tumour? J Pediatr Surg 42(12):2035–2039

Ferlito A et al (1999) Laryngeal malignant neoplasms in children and adolescents. Int J Pediatr Otorhinolaryngol 49:1–14

French CA et al (2004) Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol 22:4135–4139

Ginhart TD et al (1980) Carcinoma of the larynx in childhood. Cancer 46:1683–1688

Golledge J et al (1995) Head neck liposarcoma. Cancer 76(6):1051–1058

Holland RS et al (1998) Granular cell tumor of the larynx in a six-year-old child: case report and review of the literature. Ear Nose Throat J 77(8):652–660

Holsinger FC et al (2009) Durable long-term remission with chemotherapy alone for stage II to IV laryngeal cancer. J Clin Oncol 27:1976–1982

Joos B et al (2009) Laryngeal squamous cell carcinoma in a 13 year-old child associated with human papillmaviruses 16 and 18: a case report and review of the literature. Head Neck Pathol 3(1):37–41

Kato MA et al (1991) Rhabdomyosarcoma of the larynx in children. Med Pediatr Oncol 19(2):110–114

McWother AJ, Hoffman HT (2005) Transoral laser microsurgery for laryngeal malignancies. Curr Probl Cancer 29:180–189

Nikaghlagh S et al (2007) Rhabdomyosarcoma of the larynx. Pak J Med Sci 23(2):280–282

Pransky SM, Kang R (2003) Tumors of the larynx, trachea and bronchi. In: Bluestone CD et al (eds) Pediatric otolaryngology. Saunders, Elsevier Science, Philadelphia

Preuss SF et al (2009) Transoral laser surgery for laryngeal cancer: outcome, complications and prognostic factors in 275 patients. Eur J Surg Oncol 35(3):235–240

Pulli R, Coniglio JU (1997) Subglottic nerve sheath tumor in a pediatric patient: case report and literature review. Head Neck 19:440–444

Rahbar R et al (2003) The role of chromosomal translocation (15;19) in the carcinoma of the upper aerodigestive tract in children. Otolaryngol Head Neck Surg 129(6):698–704

Rinaldo A et al (1998) Hamarthoma of the larynx: a critical review of the literature. Ann Otol Rhinol Laryngol 107:264–267

Rodrigues M et al (2005) Inflammatory myofibroblastic tumor of the larynx in a 2-year-old male. ORL J Otorhinolaryngol Relat Spec 67:101–105

Rutherford K et al (2009) Extramedullary plasmacytoma of the larynx in an adolescent: a case report and review of the literature. Ear Nose Throat J 88(2):E1–E7

Rutt AL et al (2010) Laryngeal cancer in patients younger than 30 years: a review of 99 cases. Ear Nose Throat J 89(4):189–192

Sessions RB et al (1993) Tumours of the larynx and hypopharynx. In: DeVitta V et al (eds) Cancer: principles and practice of oncology. JB Lippincott, Philadelphia

Simon M et al (1994) Laryngeal carcinoma in a 12 year-old child. Association with human papillomavirus 18 and 33. Arch Otolaryngol Head Neck Surg 120(3):277–282

Smith RV (2008) Merck manual for healthcare professionals http://www.merckmanuals.com/professionals/sec08/ch093/ch093c.html

Smith DS et al (2004) Otolaryngologic manifestations of PHACE syndrome. Int J Pediatr Otorhinolaryngol 68(11):1445–1450

Strong MS, Jako GJ (1972) Laser surgery in the larynx. Early clinical experience with continuous CO_2 laser. Ann Otol Rhinol Laryngol 81:791–798

Vargas SO et al (2001) Upper respiratory tract carcinoma with chromosomal translocation 15;19: evidence for a distinct disease entity of young patients with a rapidly fatal course. Cancer 92:1195–1203

Part VI

Rare Tumors of the Thorax

Pathological Aspects of Mediastinal Tumors

23

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Contents

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23.1 Introduction

The mediastinum represents the space between both lungs, the diaphragm, and the vault of the thoracic cavity. It is divided in a superior, anterior, middle, and posterior compartment, each of which harbors characteristic tumors in the pediatric and adolescent age group (Fig. 23.1). Most mediastinal tumors can, however, occur in any of the mediastinal compartments due to the common occurrence of heterotopia of thymic tissue outside the anterior mediastinum.

23.2 Peculiarities of Mediastinal Tumors in Children and Adolescents

Epidemiology. Mediastinal tumors in children and adults *are rare neoplasm* (*incidence 1–5 per million children and adolescence*) *comprising 1–1.5% of tumors in this age group compared to <1% in adults* (Müller-Hermelink et al. 2004a). *Gender plays a highly variable role in the different tumors* (*see below*).

Age-Related Spectrum of Mediastinal Tumors. The relative frequency of the various thymic tumors is strikingly different in children and adolescents compared to adults (Fig. 23.2). While epithelial thymic tumors are the most common mediastinal tumors in adults, children more commonly suffer from lymphomas, followed by neurogenic tumors and germ cell tumors, while thymomas and thymic carcinomas are exceedingly rare. T-lymphoblastic lymphomas/T-ALL (acute lymphoblastic leukemia) is the predominant entity among pediatric/early adolescent lymphomas, while Hodgkin lymphomas and mediastinal large

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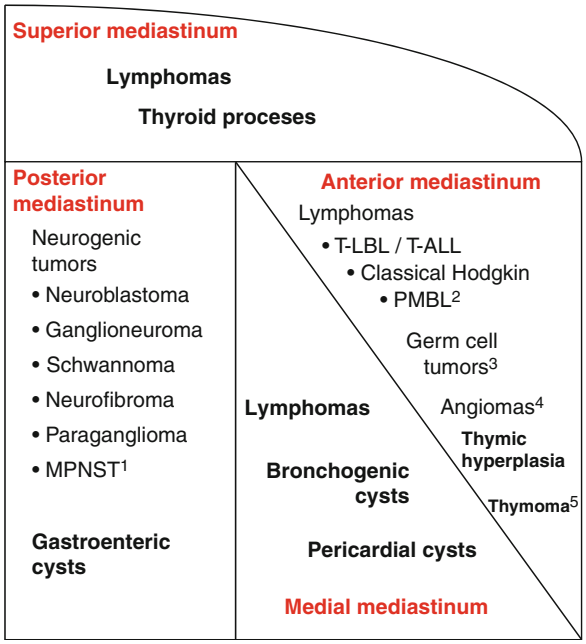

Fig. 23.1 Distribution of pediatric mediastinal tumors in the superior, anterior, middle, and posterior compartment of the mediastinum. [1]MPNST malignant peripheral nerve sheath tumors, [2]PMBL primary mediastinal large B cell lymphoma, [3]Teratomas and yolk sac tumors are the most common entities prior to puberty, [4]Angiomas comprise both hemangiomas and lymphangiomas, [5]Thymomas play no role in children and are very rare in adolescents while they are the most common mediastinal tumors in adults

B-cell lymphomas are most prevalent in late adolescence and adulthood. Among germ cell tumors, yolk sac tumors and teratomas predominate before puberty with similar frequencies in boys and girls. By contrast, seminomas, embryonal carcinomas, and mixed germ cell tumors are typical mediastinal germ cell tumors after puberty with virtual restriction to male patients.

Paraneoplastic Syndromes. Paraneoplastic syndromes are much less common in children and adolescents than in adults. This is due to the virtual absence of autoimmunity-prone thymomas in this age group (Marx et al. 2004a). Therefore, thymic pathology in a child or adolescent with seropositive myasthenia gravis (MG with autoantibodies to the acetylcholine receptor) will almost always be lymphofollicular thymic hyperplasia. A rare pediatric paraneoplastic syndrome in conjunction with a mediastinal tumor is opsomyoclonus related to neuroblastoma.

23.3 Lymphomas and Other Hematologic Malignancies

The most common mediastinal lymphomas in children and adolescents are T-lymphoblastic lymphomas (T-LBLs) (Harris et al. 2004) followed by classical Hodgkin lymphomas (cHLs) (Müller-Hermelink et al. 2004b) and primary mediastinal large B-cell lymphomas (PMBLs) (Attias et al. 2009). Rare mediastinal hematologic malignancies that occur prior to adulthood are NK cell lymphomas and myeloid malignancies. Langerhans cell histiocytosis (LCH) has to be considered as differential diagnostic possibility particularly when facing the clinical setting of "sclerosing mediastinitis." Mediastinal myeloid neoplasias including LCH may occur in isolation (Orazi 2004) or as component of mediastinal germ cell tumors (Orazi et al. 2004).

23.3.1 T-Lymphoblastic Lymphoma (T-LBL)

T-LBL is a tumor composed of immature T-cells arising in the thymus by unknown etiological factors. Immature T-cells may either exhibit immune phenotypes that are compatible with normal but arrested maturational stages of thymic T-cell development or show aberrant profiles of expressed immature T-cell markers. T-LBLs comprise about 30% of lymphomas in this age group, with a major peak of incidence between late childhood and adolescence. T-LBLs affect mediastinal and other lymph nodes in about 15% of cases. By definition, this disease is labeled as T-ALL (acute lymphoblastic leukemia of T-type) when the percentage of blasts in the bone marrow exceeds 25%. Typical clinical symptoms of T-LBL are respiratory distress, superior vena cava syndrome, and pericardial and pleural effusions.

In core needle biopsies, T-LBL shows monotonous infiltrates of small to medium-sized lymphoid blasts that commonly infiltrate beyond the thymic epithelial network and blur the normal cortico-medullary architecture of the thymus (Fig. 23.3). Epithelial cell networks are typically reduced or even absent in T-LBL. Many mediastinal T-LBLs show a regular immune phenotype corresponding to that of the major population of thymocytes that is typically TdT+, CD34(−), CD1a+, CD3+, CD5+, CD4+ in addition to CD8+, with Ki67 indices of around 90%. Other T-LBL cases may show more immature (e.g., without expression of

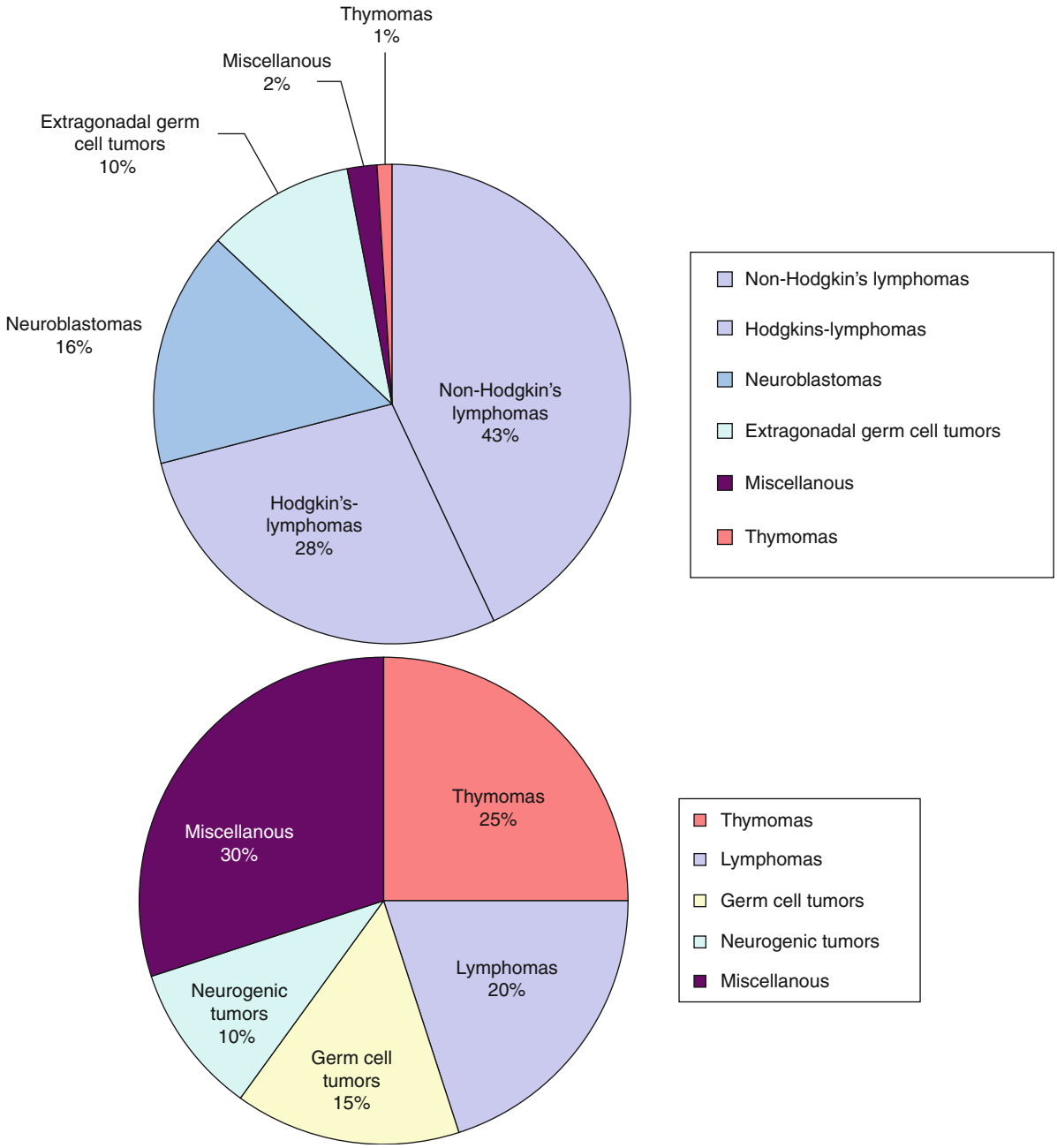

Fig. 23.2 Different proportions of the various mediastinal tumors in children and adults

CD1a) or mature phenotypes (e.g., with isolated expression of CD4 or CD8). Finally, aberrant profiles (e.g., with loss of CD5 or massive expression of CD10 and CD34) can be found as well and helpful for differential diagnostic purposes (see below). Most but not all T-LBLs show monoclonal rearrangements of T-cell receptor genes (Harris et al. 2004).

23.3.2 Differential Diagnosis of T-LBL

(a) *True thymic hyperplasia* (*TTH*) is a rare finding of unknown pathogenesis mostly in infants and young children who may suffer from respiratory and cardiac failure that commonly require emergency interventions. Biopsies of sufficient size

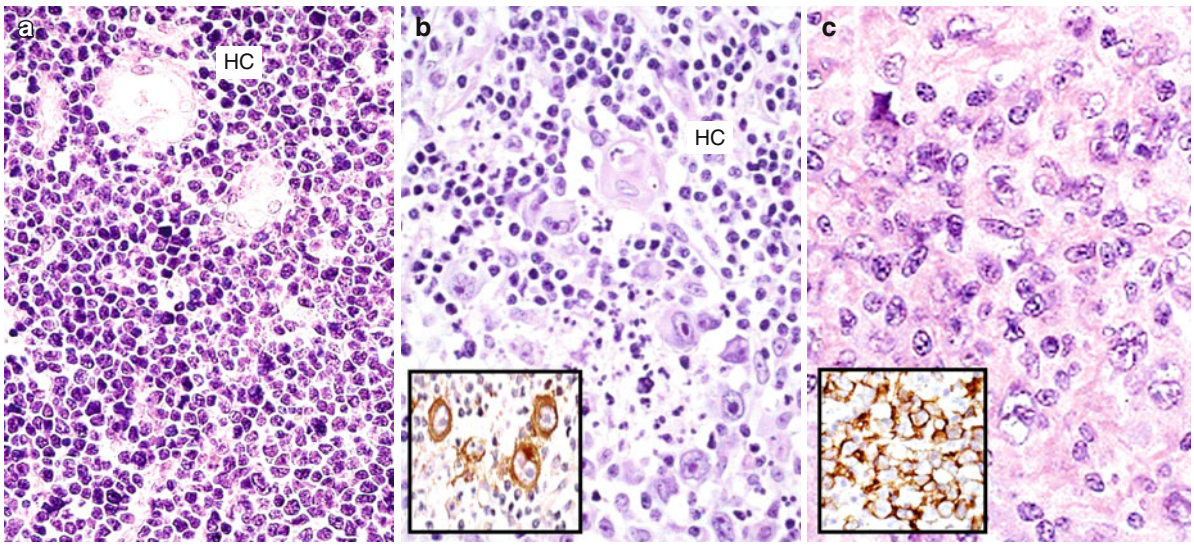

Fig. 23.3 Histology of the main lymphoma subtypes encountered in children. (**a**) T-lymphoblastic lymphoma. Monotonous medium-sized blasts infiltrating adjacent to Hassall corpuscle (*HC*). (**b**) Classical Hodgkin lymphoma of the thymus, infiltrating adjacent to Hassall corpuscle (*HC*). Inset: CD30 expression in Hodgkin cells. (**c**) Primary mediastinal B-cell lymphoma. Infiltrate of pleomorphic tumor cells, some resembling Hodgkin cells. Inset: consistent strong expression of CD20 in all tumor cells

show a normal cortico-medullary architecture and normal T-cells subsets. In small biopsies or on aspiration cytology, the distinction between TTH and T-LBL can be very difficult, particularly when the neoplastic immature T-cells of T-LBL show a normal immune phenotype. Detection in most T-LBLs but not TTH of reduced epithelial cells by immunohistochemistry and of monoclonal rearrangement of T-cell receptor genes can be helpful. Intrathymic bleeding is a life-threatening complication in children (Eifinger et al. 2007).

(b) *Rebound hyperplasia* represents a tumor-like "over-shooting" regeneration of the thymus commonly between 2 and 12 months (rarely even much later) after the end of chemotherapy or steroid treatment, raising the question of local tumor recurrence in case of mediastinal tumors. Taking clinical history and the lack of clinical symptoms into account, biopsies can generally be avoided or postponed. In equivocal cases, biopsy may be required to clarify the situation: histology then reveals normal thymic tissue and polyclonal rearrangement of T-cell receptor genes. Of note, increased tracer uptake as revealed by thallium scintigraphy or FDG-PET-CT is not usually helpful to distinguish tumor recurrence from rebound thymic hyperplasia (Margery et al. 2007; Roebuck et al. 1998).

(c) *Lymphoid follicular thymic hyperplasia*, *TFH*, is an inflammatory thymic alteration ("*thymitis*"), due to accumulation of B-cell-rich lymphoid follicles (mostly with formation of germinal centers) in so-called perivascular spaces within the destructed thymic medulla. Thymic cortex is apparently unaltered in TFH. The triggers of TFH are unknown. TFH is the typical thymic alteration in children and adults with seropositive "early onset myasthenia gravis" (i.e., in patients younger than 50 years of age with antiacetylcholine receptor autoantibodies). Less commonly, TFH can occur in rheumatoid arthritis, autoimmune thyroid disease and other autoimmune states (Ströbel et al. 2009).

(d) *Thymomas* enter the differential diagnosis of T-LBL because they also usually harbor immature T-cells in adolescents (see below).

23.3.3 Primary Mediastinal B-Cell Lymphoma (PMBL)

PMBL is a lymphoma of unknown etiology that typically occurs in early adulthood but rarely also in adolescents, mainly females with a mean age of 14 years at first diagnosis. PMBL is thought to derive from normal thymic medullary B-cells. PMBL is typically localized in the anterior mediastinum and commonly

elicits superior vena cava syndrome. Diagnosis usually requires (CT-guided) core biopsies. Histopathology is highly variable. Stromal sclerosis and large, clear tumor cells are classical findings, but a broad spectrum of morphological variants (including Hodgkin-like tumor cells) have been described. Their eventual cohesive growth pattern can mimic carcinomatous infiltrates (Abb.3). By immunohistochemistry, most cases show the following profile: CD20+ CD23+/– CD30+/– CD45+ CD15– CD5– HLA–DR–. There is no EBV association (LMP1 and EBER are negative) (Schmitz et al. 2011; Attias et al. 2009). Distinction from classical Hodgkin lymphoma can be difficult, and true "gray zone lymphomas" have been described as well (Oschlies et al. 2011). Like T-LBL and other lymphomas, PMBL is not associated with myasthenia gravis.

23.3.4 Differential Diagnosis of PMBL

The most difficult distinction concerns classical Hodgkin lymphoma (HL). Tumor cells of HL can sometimes express CD20 (like PMBL) but are commonly negative for D79a and CD45. Rarely, diffuse large B-cell lymphomas (DLBLs) and B-lymphoblastic lymphomas/B-ALL can arise within the mediastinum (Gaulard et al. 2008; Jaffe et al. 2008). Low-grade B-cell lymphomas (e.g., MALT lymphomas) are virtually nonexistent in children. By contrast, pediatric Castleman disease is a diagnostic option in case of solitary, tumor-like, hyperemic B-cell-rich mediastinal processes.

23.3.5 Hodgkin Lymphoma (HL)

HL within the mediastinum can primarily arise from thymus (Fig. 23.3) or mediastinal lymph nodes. Mediastinal HL typically belongs to the "classical" subset (nodular sclerosis predominates over mixed cellularity cases), while "nonclassical," lymphocyte-predominant HL ("paragranuloma") is virtually nonexistent in the mediastinum. Tumor cells in classical HL of children and adolescents exhibit the same immune profile as in adults: CD30+ CD15+/– CD20–/+ PAX5+ CD45– CD23–/+ EMA–. Expression of EBV-related LMP1 or RNA (EBER) occurs in 50% of cases (Müller-Hermelink et al. 2004b). The differential diagnosis comprises PMBL (Gaulard et al. 2008) and, rarely, cytotoxic CD30+ CD45+ EMA+ CD15– CD20– PAX5– Anaplastic Large T-cell Lymphoma (ALCL) that is usually Alk1(+) in children and adolescents (Le Deley et al. 2008).

23.4 Germ Cell Tumors (GCTs)

In general, mediastinal GCTs in children and adults exhibit the same histological features as their counterparts in adults and in testis or ovaries (Wick et al. 2004a). A rare but specific finding in mediastinal teratomas in both children and adults is a pancreatic tissue component. The various subtypes of GCT occur at significantly different frequencies before and after puberty (Table 23.1). Teratomas and yolk sac tumors are the only GCTs occurring before puberty at relevant frequency (Edward et al. 2009; Perlman et al. 2004; Wick et al. 2004b) (Fig. 23.4). By contrast, postpubertal GCTs resemble their counterparts in adults, including seminoma, embryonal carcinoma, and mixed GCTs. Interestingly this age-related difference of histotypes is mirrored by molecular features: before puberty, genetic losses (1p, 5q, 6p), and gains (1q, tetraploidy) are characteristic for nonteratomatous GCT, while presence of isochromosome 12p (in 70% of cases) and aneuploidy are typical alteration after puberty (Wick et al. 2004a). Teratomas are subclassified as either mature or immature according to their content of immature tissue components; immature components typically represent fetal neuroectodermal structures (Wick et al. 2004b), as shown in Fig. 23.4.

23.5 Neurogenic Tumors

Neuroblastomas (NBs) are typically localized in the posterior mediastinum and count among the most common mediastinal tumors in children (Fig. 23.4). Ganglioneuroblastomas and ganglioneuromas are found in slightly older children and even young adults than in children with neuroblastomas; they also preferentially occur in the posterior mediastinum (Joshi 2000). Neurogenic tumors rarely occur inside the thymus (Marx et al. 2004b).

A minority of benign and less commonly malignant paragangliomas ("pheochromocytomas") occur in the posterior mediastinum. Occurrence of paragangliomas in children can be a hint to "Carney complex" or mutation of the succinate dehydrogenase gene (Stratakis and Carney 2009).

Table 23.1 Mediastinal germ cell tumors (GCTs) in relation to puberty of children and adolescents

Age at diagnosis	Histology	Gender	Clinical course	Immune phenotype of tumor cells (Liu et al. 2010; McKenny et al. 2007; Perlman and Hawkins 1998)
Before puberty	Teratoma (immature; mature)	M = F	Usually favorable (if resectable)	Variable, dependant on composition; EMA+; glypican 3 in immature neural elements +
	Yolk sac tumor	F > M	Malignant	AFP+; cytokeratin+; EMA−; glypican 3 +
After puberty	Teratoma (immature; mature)	M >>> F	Usually favorable	Variable, depends on composition; EMA++; glypican 3 in immature neural elements +
	Seminoma	M >>> F	Malignant	CD117 (= KIT)+; PLAP+; OCT4+; D2–40+ in 70%; cytokeratins+; βHCG may be expressed in single syncytiotrophoblastic cells, but AFP is −
	Yolk sac tumor	M >>> F	Malignant	AFP+, cytokeratin+, EMA−; CD30−; +; glypican 3+
	Embryonal carcinoma	M >>> F	Malignant	CD30+/+++ cytokeratin+; CD117−; AFP−/+
	Choriocarcinoma	M >>> F	Malignant	βHSG+++, CD30(+); cytokeratin +
	Mixed GCTs	M >>> F	Malignant	Dependant on composition
	GCT with somatic type malignancy	M >>> F	Malignant	Dependant on the type of GCT-derived carcinoma, sarcoma, or leukemia

Postpubertal GCTs are often associated with Klinefelter syndrome
Gender (*M* male, *F* female), *AFP* α-fetoprotein, *CD117* cluster of differentiation 117 (= KIT, stem cell factor receptor), *PLAP* placental alkaline phosphatase, *Oct-4* octamer binding transcription factor-4, *D2-40* Podoplanin, *βHCG* human chorionic gonadotropin, *EMA* epithelial membrane antigen

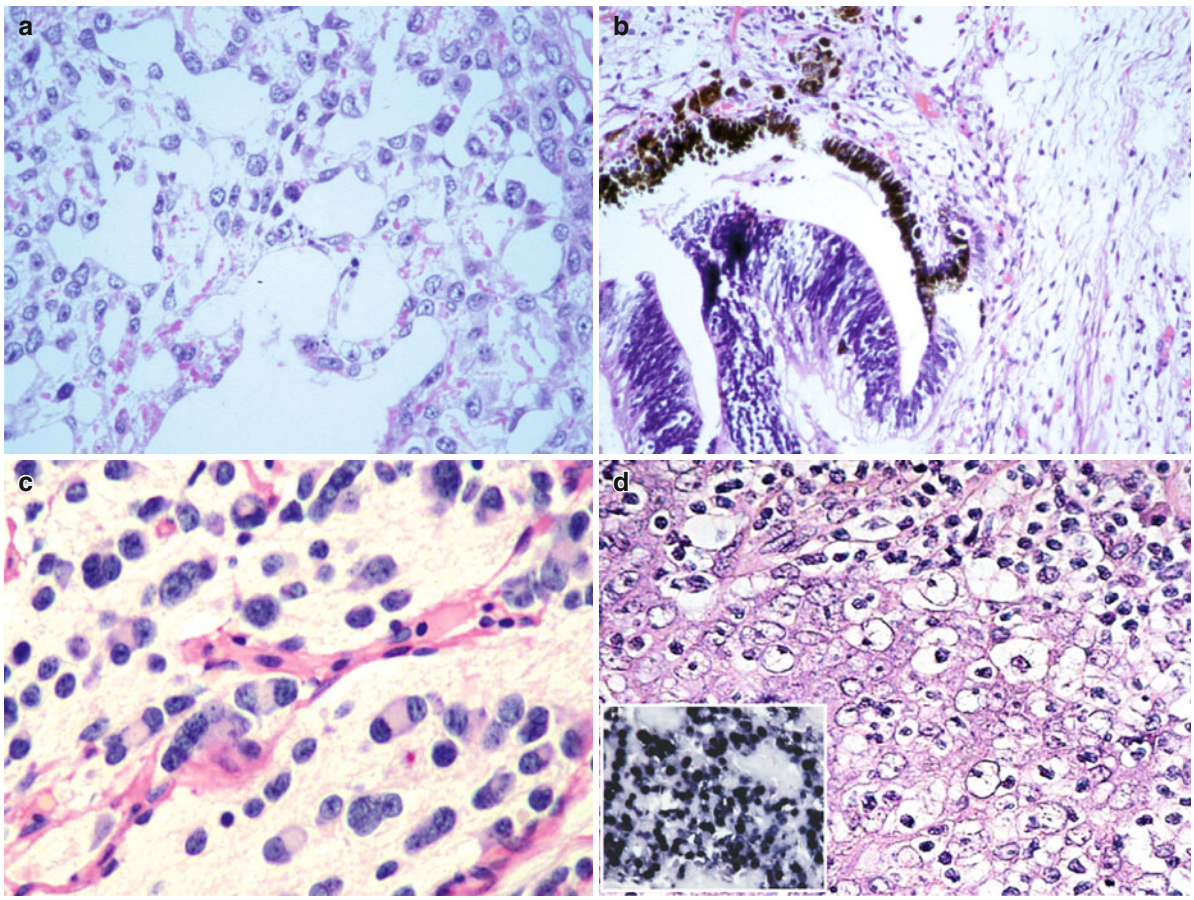

Fig. 23.4 Histology of solid mediastinal tumors occurring in children and adolescents. (**a**) Yolk sack tumor, the common non-teratomatous tumor before puberty. (**b**) Immature teratoma showing immature neuroectodermal tissue (retinal pigment epithelium). (**c**) Neuroblastoma (differentiating), a typical tumor of the posterior mediastinum in children and adolescents. (**d**) Lymphoepithelioma-like carcinoma of the thymus (inset: EBER in situ hybridization, revealing Epstein–Barr virus RNA)

23.6 Mesenchymal Tumors

Mesenchymal tumors of the mediastinum are rare in children and adults, except for lymphangiomas and (mostly cavernous) hemangiomas. Lipomas, lipoblastomatosis, well differentiated and, less common, myxoid liposarcomas, benign and malignant nerve sheath tumors (including triton tumors in association with neurofibromatosis), hemangioendothelioma and angiosarcoma, low-grade fibromyxoid sarcoma, rhabdoid tumors, and rhabdomyosarcoma of embryonal and alveolar type have been described as derivatives of mediastinal soft tissue (Ayadi and Khabir 2010; Amra and Amr 2009; Fernandez et al. 2009; Garces-Inigo et al. 2009; Steiner et al. 2009; Marx et al. 2004b).

Ewing family tumors (including the peripheral primitive neuroectodermal tumors (pPNETs)), synovial sarcomas, chondrosarcomas, and osteosarcomas in the mediastinum usually arise from the sternum or thoracic wall and show the same immunohistochemical and genetic alterations as their extramediastinal counterparts (Marx et al. 2004b).

Every sarcoma in the mediastinum of a child or adolescent should arouse suspicion of an underlying "teratoma mit somatic type malignancy" (Wick et al. 2004c).

23.7 Thymomas and Thymic Carcinomas

Thymomas are tumors of thymic epithelial cells with preservation of thymus-like features (in contrast to thymic carcinomas). Consequently, thymomas almost always harbor immature, TdT+ T-cells that show the normal immune phenotype of cortical thymocytes, i.e., expression of CD1a, CD3, CD5, and both CD4 and CD8. According to the WHO classification, they are divided into types A, AB, B1, B2, and B3 thymomas based on the morphology of neoplastic epithelial cells and the content of immature T-cells. Almost all thymomas in children and adolescents are B2 and B3 types that commonly behave in a clinically malignant fashion.

Of note, thymomas are so exceedingly rare in children and adolescents that other more likely diagnoses have to be excluded before accepting a diagnosis of pediatric thymoma, particularly when it relies on small (core or fine needle aspiration) biopsies. Among lymphocyte-rich TDT+lesions, true thymic hyperplasia is a much more likely diagnosis in newborns and children, while T-LBL and thymic hyperplasias (see above) are much more common than thymomas in children and adolescents. Thymomas are usually distinguished from these alternative pathologies by an increased content of cytokeratin-positive neoplastic thymic epithelial cells; in addition, abnormal T-cell immune phenotypes and monoclonal T-cell receptor rearrangement are common (but inconsistent) features of T-LBL (see above). Another diagnostic pitfall in lymphocyte-poor, spindle cell tumors is the interpretation of mediastinal synovial sarcoma as type A thymoma; while the former is well described in children and adolescents (Marx et al. 2004b), the latter is virtually nonexistent in this age group.

Thymic carcinomas (*TCs*) are also very rare tumors in children. The epithelial cells of TCs show marked atypia and – in contrast to thymomas in young people – are *not* accompanied by immature (TdT+) T-cells. The most common TCs in children and adolescents are lymphoepithelioma-like TCs that typically show large cell features and accompanying inflammatory infiltrates of *mature*, *TdT*(−) T- cells, B-cells, and plasma cells and are almost always EBV-associated, as revealed by EBER in situ hybridization (Kuo et al. 2004) (Fig. 23.4). Less common TCs are squamous cell carcinomas, neuroendocrine carcinomas, and so-called NUT midline carcinomas. The latter are highly aggressive cancers that either look like undifferentiated carcinomas or poorly differentiated squamous cell carcinomas. They are characterized by translocations of the NUT gene (on chromosome 15q14) and most commonly involve the BRD4 gene as fusion partner due to a t(15;19)(q13;p13.1) translocation (French 2010).

23.8 Mediastinal Cysts

Although cysts are no tumors, they are mentioned here because some of them can be "indicator" of underlying neoplasia or inflammation. Among cysts, unilocular cysts are often congenital. They comprise brochogenic cysts that are the commonest (50%), showing ciliated or squamous epithelial cells as inner lining; pleuropericardial cysts that are lined by mesothelial cells (30% of cases), and thymic cysts (15% of cases) that reveal squamous or cuboidal epithelial lining cells and thymic lymphoid tissue inside or adjacent to the cyst wall. In contrast to unilocular cysts, multilocular cysts are commonly acquired and associated with thymitis, lymphadenitis (including tuberculosis), Hodgkin lymphoma, germ cell tumors, Langerhans cell histiocytosis, and

thymic epithelial tumors (Le Pimpec-Barthes et al. 2010). Cysts have to be distinguished from cystic tumors, including teratomas and cystic lymphangiomas, the latter showing cavities lined by atypia-free endothelial cells.

References

Amra NK, Amr SS (2009) Mediastinal lipoblastomatosis: report of a case with complex karyotype and review of the literature. Pediatr Dev Pathol 12:469–474

Attias D, Hodgson D, Weitzmann S (2009) Primary mediastinal B-cell lymphoma in the pediatric patient: can a rational approach to therapy be based on adult studies? Pediatr Blood Cancer 52(5):566–570

Ayadi L, Khabir A (2010) Pediatric angiosarcoma of soft tissue: a rare chlinicopatholoic entity. Arch Pathol Lab Med 34(3):481–485

Edward M, Barksdale J, Obokhare I (2009) Teratomas in infants and children. Curr Opin Pediatr 21:344–349

Eifinger F, Ernestus K, Benz-Bohm G, Körber F, Hünseler C, Hekmat K, Marx A, Roth B (2007) True thymic hyperplasia associated with severe thymic cyst bleeding in a newborn: case report and review of the literature. Ann Diagn Pathol 11:358–362

Fernandez Y, Bernabeu-Wittel M, Garcia-Morillo JS (2009) Kaposiform hemangioendothelioma. Eur J Intern Med 20(2): 106–113

French CA (2010) NUT midline carcinoma. Cancer Genet Cytogenet 203(1):16–20

Garces-Inigo EF, Leung R, Sebire NJ, McHugh K (2009) Extrarenal rhabdoid tumours outside the central nervous system in infancy. Pediatr Radiol 39(8):817–822

Gaulard P, Harris NL, Pileri SA, Kutok JL, Stein H, Kovrigina AM, Jaffe ES, Möller P (2008) Primary mediastinal (thymic) large B-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds) WHO classification of tumours of the haematopoietic and lymphoid tissues. IARC Press, Lyon, pp 250–251

Harris NL, Borowitz M, Jaffe ES, Vardiman JW (2004) Precursor T-lymphoblastic lymphoma/leukaemia. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 227–228

Jaffe ES, Stein H, Swerdlow SH, Campo E, Pileri SA, Harris NL (2008) B-cell lymphomas, unclassifiable with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds) WHO classification of tumours of the haematopoietic and lymphoid tissues. IARC Press, Lyon, pp 267–268

Joshi VV (2000) Peripheral neuroblastic tumors: pathologic classification based on recommendations of international neuroblastoma pathology committee (modification of shimada classification). Pediatr Dev Pathol 3:184–199

Kuo TT, Chan JKC, Mukai K, Eimoto T, Tateyama H (2004) Lymphoepithelioma-like carcinoma. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 177–178

Le Deley MC, Reiter A, Williams D, Delsol G, Oschließ I, McCarthy K, Zimmermann M, Brugières L (2008) Prognostic factors in childhood anaplastic large cell lymphoma: results of a large European intergroup study. Blood 111:1600–1606

Le Pimpec-Barthes F, Cazes A, Bagan P, Badia A, Vlas C, Hernigou A, Pricopi C, Riquet M (2010) Mediastinal cysts: clinical approach and treatment. Rev Pneumol Clin 66(1):52–62

Liu A, Cheng L, Du J, Peng Y, Allan RW, Wei L, Li J, Cao D (2010) Diagnostic utility of novel stem cell markers SALL4, OCT4, NANOG, SOX2, UTF1, and TCL1 in primary mediastinal germ cell tumors. Am J Surg Pathol 34:697–706

Margery J, de Revel T, Magois E, Bonardel G, Leduc I, Saint-Blancard P, Bonnichon A, Vaylet F, Jancovici R, Nedellec G (2007) Filling the thymic space after treatment of Hodgkin's disease: rebound or relapse. Rev Pneumol Clin 63:45–47

Marx A, Ströbel Ph, Zettl A, Chan JKC, Müller-Hermelink HK, Harris NL, Kuo TT, Shimosato Y, Engel P (2004a) Thymomas. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 152–153

Marx A, Kuo TT, Strobel P, Zhang PJ, Shimosato Y, Chan JKC (2004b) Soft tissue tumours of the thymus and mediastinum. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 239–245

McKenny JK, Heerema-McJenny A, Rouse RV (2007) Extragonodal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and different diagnostic considerations. Adv Anat Pathol 14:69–92

Müller-Hermelink HK, Engel P, Kuo TT, Ströbel Ph, Marx A, Harris NL, Möller P, Menestrina F, Shimosato Y, Asamura H, Masaoka A, Sobin LH (2004a) Tumours of the thymus: introduction. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 148–151

Müller-Hermelink HK, Rüdiger T, Harris NL, Jaffe ES, Rosenwald A, Chan JKC (2004b) Hodgkin lymphoma of the mediastinum. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 230–232

Orazi A (2004) Myeloid sarcoma and extramedullary acute myeloid leukaemia. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics, tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, p 238

Orazi A, Wick MR, Hartmann JT, Marx A (2004) Germ cell tumours with associated haematologic malignancies. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 207–208

Oschlies I, Burkhardt B, Salaverria I, Rosenwald A, d'Amore ES, Szczepanowski M, Koch K, Hansmann ML, Stein H, Möller P, Reiter A, Zimmermann M, Rosolen A, Siebert R, Jaffe ES, Klapper W (2011) Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica. 96:262–268

Perlman EJ, Hawkins EP (1998) Pediatric germ cell tumors: protocol update for pathologists. Pediatr Dev Pathol 1:328–335

Perlman EJ, Marx A, Bokemeyer C, Wick MR (2004) Yolk sac tumour. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 207–208

Roebuck DJ, Nicholls WD, Bernard EJ, Kellie SJ, Howman-Giles R (1998) Misleading leads. Thallium-291 uptake in rebound hyperplasia. Med Pediatr Oncol 30:297–300

Schmitz R, Hansmann ML, Bohle V, Martin-Subero JI, Hartmann S, Mechtersheimer G, Klapper W, Vater I, Giefing M, Gesk S, Stanelle J, Siebert R, Küppers R (2009) TNFAIP3 (A20) is a tumor suppressor gene in Hodgkin lymphoma and primary mediastinal B cell lymphoma. J Exp Med. 206: 981–989

Steiner MA, Giles HW, Daley WP (2009) Massive low-grade fibromyxoid sarcoma presenting as acute respiratory distress in a 12-year-old girl. Pediatr Radiol 39(4):396–399

Stratakis CA, Carney JA (2009) The triad of paragangliomas, gastric stromal tumours and pulmonary chondromas (Carney triad), and the dyad of paragangliomas and gastric stromal sarcomas (Carney-Stratakis syndrome): molecular genetics and clinical implications. J Intern Med 266:43–52

Ströbel P, Moritz R, Leite MI, Willcox N, Chuang WY, Gold R, Nix W, Schalke B, Kiefer R, Müller-Hermelink HK, Jaretzki Iii A, Newsom-Davis J, Marx A (2009) The ageing and myasthenic thymus: a morphometric study validating a standard procedure in the histological workup of thymic specimens. J Neuroimmunol 201–202:64–73

Wick MR, Perlman EJ, Orazi A, Müller-Hermelink HK, Zettl A, Göbel U, Bokemeyer C, Hartman JT, Marx A (2004a) Germ cell tumours of the mediastinum. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 198–201

Wick MR, Perlmann EJ, Göbel U, Schneider DT, Ströbel P, Chan JCK, Marx A (2004b) Teratoma. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 210–212

Wick MR, Perlmann EJ, Ströbel Ph, Chan JKC, Marx A (2004c) Germ cell tumours with somatic-type malignancy. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (eds) World Health Organization classification of tumours. Pathology and genetics tumours of the lung, pleura, thymus and heart. IARC Press, Lyon, pp 216–218

Mediastinal Germ Cell Tumors

24

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24.1 Introduction

The general aspects of germ cell tumors common to all germ cell tumors occurring at different sites are discussed in the chapters of gonadal germ cell tumors (see Chap. 39). In the thorax, germ cell tumors almost exclusively develop in midline locations, mostly in the anterior mediastinum. Therefore, it has been debated whether such extragonadal germ cell tumors, in particular teratomas may originate from midline somatic stem cells. On the other hand, there is molecular evidence that both gonadal and extragonadal germ cell tumors indeed originate from primordial germ cells at different stages of development. Thus, the examination of the epigenetic control of genomic imprinting reveals a methylation pattern that is characteristic of primordial germ cells during and shortly after their migration during early embryonal development (Schneider et al. 2001b; Bussey et al. 2001). In addition, this methylation pattern distinguishes germ cell tumors from other embryonal tumors with presumed stem cell origin such as nephroblastoma (Sievers et al. 2005), thus substantiating the hypothesis of their specific germ cell origin.

Some important age-dependent biologic patterns can be observed in mediastinal germ cell tumors (Schneider et al. 2002a, 2004). These are helpful for both diagnosis and prognostic assessment and therefore treatment planning. In young adults, mediastinal germ cell tumors belong to the most frequent extragonadal germ cell tumors, contributing approximately 10% to all germ cell tumors. Of note, malignant mediastinal germ cell tumors develop almost exclusively in males, while in females, only rare teratomas are diagnosed. Individuals with a constitutional Klinefelter

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(47, XXY) karyotype have a significantly increased risk of developing germ cell tumors, in particular malignant nonseminomatous germ cell tumors, and they tend to develop them at a significantly younger age (Nichols et al. 1987).

In adults, malignant mediastinal germ cell tumors, in particular nonseminomatous tumors tend to have a poor prognosis with approximately 50% long-term survival, even with intensive multimodal therapy (Hainsworth 2002; Ganjoo et al. 2000). Adult mediastinal germ cell tumors frequently include significant proportions of yolk sac tumor and/or choriocarcinoma. Although the corresponding tumor markers alpha 1-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) may be helpful for diagnosis, high levels of AFP and β-HCG are associated with poor prognosis (Group, IGCCC 1997). In particular, mediastinal choriocarcinoma are frequently associated with widespread metastases including metastases to the central nervous system, which also bear a dismal prognosis.

Moreover, this unfavorable prognosis of malignant nonseminomatous germ cell tumors is also related to their ability to give rise to malignancies of non-germ cell histology such as leukemia and sarcoma (Nichols et al. 1990; Motzer et al. 1998; Donadio et al. 2003; Fizazi et al. 1998). It has been demonstrated that these secondary malignancies also display genetic aberrations that prove their origin from the malignant germ cell tumor (Chaganti et al. 1989; Oosterhuis et al. 1991; Orazi et al. 1993). In a multi-institution review, Hartmann et al. reported secondary hematologic malignancies in approximately 2% of adult patients with mediastinal nonseminomatous germ cell tumor (Hartmann et al. 2000). In contrast, such malignancies have been reported only rarely in association with gonadal tumors; in some of these cases, affected patients have been shown to have some form of XY gonadal dysgenesis (Kaplan et al. 1991; Koo et al. 1992).

Adult malignant mediastinal germ cell tumors display the characteristic genetic hallmark of adult testicular germ cell tumors, the isochromosome 12p or 12p amplification, respectively (Chaganti and Houldsworth 1998). For further details, see Part VIII.

During childhood, the anterior mediastinum belongs to the less frequent anatomic sites of childhood germ cell tumors, accounting to approximately 5% of all childhood germ cell tumors (Schneider et al. 2004; Billmire et al. 2001). Mediastinal germ cell tumors

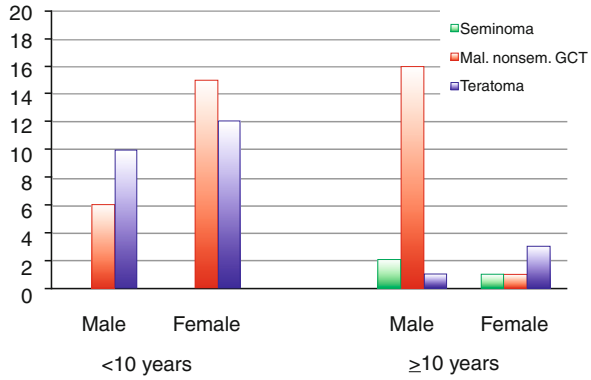

Fig. 24.1 Distribution of histologic subtypes according to age

occurring during childhood show a clinical and biologic profile that is distinct from the corresponding tumors of adolescents and adults. During childhood, malignant germ cell tumors show a slight female preponderance and are exclusively composed of yolk sac tumor, sometimes admixed with teratoma (Schneider et al. 2002a) (Fig. 24.1). This makes the AFP an exquisite tumor marker in tumors of the anterior mediastinum (Schneider et al. 2001). If the age-related reference values are considered and disorders associated with elevated AFP levels are excluded (Blohm et al. 1998; Schneider et al. 2001), an increased AFP level will prove a significant yolk sac tumor component in an anterior mediastinal tumor.

Biologically, germ cell tumors developing prior to the onset of puberty are distinct from mediastinal germ cell tumors in young men. Teratomas show no apparent chromosomal imbalances, and malignant YSTs show imbalances at 1p, 6q, and 20q, comparable to the pattern observed in gonadal germ cell tumors of this age group, while they lack 12p aberrations (Schneider et al. 2002b). Moreover, mediastinal germ cell tumors developing in children are not associated with secondary malignancies, and prognosis if overall favorable, comparable to that at other nongonadal sites. Accordingly, childhood germ cell tumors less frequently metastasize into the CNS.

24.2 Clinical Diagnosis

Adolescents with germ cell tumors in the anterior mediastinum are often relatively asymptomatic; whereas, infants and toddlers more often exhibit severe

Table 24.1 Specific diagnostic strategy in anterior mediastinal tumors, suspicious of germ cell tumors

Procedure	Specific questions
Clinical assessment	
Physical examination	Signs of upper airway obstruction, vena cava superior syndrome
	Pubertal status, signs of Klinefelter
	Gonadal primary
Laboratory assessment	
– AFP, β-HCG	Malignant germ cell tumor with yolk sac tumor or choriocarcinoma
– HPLAP	Malignant seminomatous germ cell tumor
– LDH	Unspecific marker with prognostic impact
– Catecholamines	Exclusion of neuroblastoma
– Blood count (bone marrow bx.)	Exclusion of hematologic malignancy(in adolescents and adults)
– Cytogenetics	Exclude Klinefelter syndrome (boys)
– Pregnancy test	Exclude pregnancy. If β-HCG is elevated, perform pelvic ultrasound to exclude pregnancy
Radiographic assessment	
Chest CT (alt. + chest MRI)	Site, organ of origin, cystic structures or calcification (teratoma), mediastinal metastases, lung metastases
Abdominal ultrasound	Liver metastases, lymph node metastases,testicular primary
CNS-MRI	CNS metastases (mandatory in choriocarcinoma)
Bone scan	Skeletal metastases (indicated in case of bone pain)
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)
β-HCG	Choriocarcinoma
CD-30	Embryonal carcinoma
OCT3/4	Seminoma (embryonal carcinoma)

respiratory symptoms, including hemoptysis or upper airway obstruction (Schneider et al. 2000). Some patients may develop vena cava superior obstruction. The clinical presentation is not strictly associated with histology and biology. Thus, even "benign" teratomas my present with life-threatening complications. In such situations, the tumor markers AFP and β-HCG should be utilized immediately to guide clinical diagnosis and weigh the therapeutic options, especially whether immediate chemotherapy could be chosen to alleviate symptoms and to avoid immediate surgery with general anesthesia. The tumor markers AFP and β-HCG are also helpful in distinguishing secreting germ cell tumors from anterior mediastinal tumors with different histogenesis such as thymoma or lymphoma (Grosfeld et al. 1994)

Seminomas may be associated with elevated levels of human placenta like alkaline phosphatase (HPLAP). However, this marker has not yet been widely studied in mediastinal seminomas. Large tumors may be associated with elevated lactate dehydrogenase (LDH), which is a rather unspecific marker of tumor burden. But if LDH is significantly elevated, it may serve as an additional prognostic marker (Group, IGCCC 1997; Frazier et al. 2008).

By the use of the tumor markers AFP and β-HCG, diagnostic delay by biopsy can be avoided. Considering the histologic heterogeneity of germ cell tumors, the diagnostic contribution of fine needle biopsy is mainly confirmatory and always has to be interpreted in the context of clinical tumor markers (Goel et al. 2008). It may be used in marker negative tumors, in particular if thymoma, lymphoma, or other mediastinal malignancies have to be excluded. In all other tumors that are considered assessable to complete resection based on radiographic imaging, primary complete resection should be attempted as an initial both diagnostic and therapeutic step (Table 24.1).

Radiographic imaging of mediastinal germ cell tumors commonly displays a tumor within or in close proximity to the thymus. Often invasion of the pericardium or pleura is observed, which may be associated with pericardial or pleural effusion. Teratomas tend to have cystic structures, occasional calcification, as well as

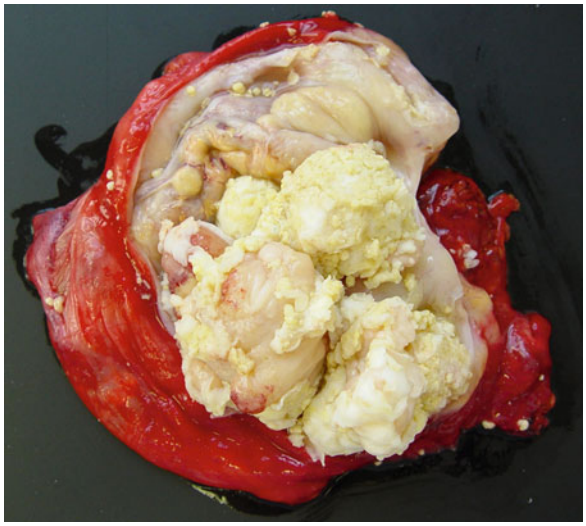

Fig. 24.2 Cystic mediastinal teratoma of a young woman

lipid rich tissue (Priola et al. 2006) (Fig. 24.2). Mediastinal lymph nodes may be enlarged in case of metastases, and in malignant germ cell tumors, lung metastases may be detected by CT. Choriocarcinoma have a significant tendency to metastasize into the central nervous system (Göbel et al. 2010). Therefore, a brain MRI has to be performed in every patient with elevated β-HCG or even the slightest neurological symptoms. Other metastatic sites may include the liver and rarely the bones.

During infancy and young childhood, the histologic subtypes are almost exclusively restricted to teratoma and yolk sac tumor. After the onset of puberty, histologic subtypes include most commonly yolk sac tumor, germinoma, choriocarcinoma, teratoma, and immature teratoma either alone or as mixed elements (Schneider et al. 2002a). Mediastinal teratomas occasionally have sarcomatous foci-resembling rhabdomyosarcoma, angiosarcoma, or undifferentiated sarcoma. These foci are extremely aggressive, tend to overgrow the remaining teratoma, and make treatment very difficult. In adolescents and adults, malignant germ cell tumors, usually with a yolk sac tumor component, may also be associated with hematopoietic malignancies.

24.3 Therapy

As in other sites, therapy of mediastinal germ cell tumors follows a multimodal approach. In pure teratomas, the complete resection constitutes the most important therapeutic step (Schneider et al. 2000; Billmire et al. 2001). In pure teratomas, there is no role for adjuvant chemo- or radiotherapy; only in large and irresectable tumors, an individual attempt may be made, however, with only minimal prospect of response to chemotherapy (Schneider et al. 2000). However, it should be considered that malignant germ cell tumors may include benign teratoma components. These may then response incompletely to preoperative chemotherapy. In such situations, an attempt of delayed complete surgical resection should be taken even in bulky tumors (Billmire et al. 2001). Fortunately, compared to other nongonadal sites such as the coccygeal region, the risk of relapse after microscopically incomplete resection appears to be less, indicating yet unknown environmental factors that may influence the risk of recurrence. Nevertheless, the surgical approach in a marker negative tumor in which the radiographic assessment is suggestive of teratoma should always aim for a complete resection.

24.4 Principles of Surgical Resection of Mediastinal Germ Cell Tumors

Mediastinal germ cell tumors are mainly found in the anterior compartment, in direct contact with the thymus. The initial surgical approach depends on the likelihood of malignancy of the mass and the feasibility of a safe primary excision. A biopsy should be undertaken when a malignant germ cell tumor is suspected and if imaging investigations show an unresectable mass and if the patient is not jeopardized by the biopsy.

Biopsy technique options include open technique using the Chamberlain anterior approach (Olak 1996) or image-guided tru-cut biopsy. If the CT scan shows compression of the major airways and vena cava, an accurate assessment of the anesthetic risk is needed: actually, respiratory collapse and cardiopulmonary arrest on induction of general anesthesia are well-recognized complications also for a biopsy of an anterior mediastinal mass (Shamberger et al. 1991). Therefore, the patients must not be put at risk if the diagnosis of a malignant germ cell tumor can be established based on tumor markers and imaging.

Teratomas are also found in the pericardium, and the patient may present with cardiac tamponade. These tumors often have a stalk to the great vessels and

compress the atria. Treatment requires complete resection (Gobbi et al. 2007; Schneider et al. 2000).

Initial or delayed resection of germ cell tumors can be performed by a posterolateral thoracotomy or a sternotomy depending upon the extension of the disease. In some patients, partial resection of the pericardium or a partial or total thymectomy has to be performed (Schneider et al. 2000).

24.5 Multimodal Therapy in Malignant Germ Cell Tumors

In secreting tumors, diagnosis can be established based on imaging and tumor markers. By definition, secreting tumors are always malignant. Prognosis is associated with histology and age at presentation. In childhood yolk sac tumors, favorable outcome can be achieved with four cycles of platinum-based three-agent chemotherapy such as PEB, PEI, or JEB (see Table 39.4).

Ideally, chemotherapy should be given up-front after establishment of the clinical diagnosis based on tumor markers. Thus, complete resection may be facilitated on delayed surgery, e.g., after three cycles of chemotherapy. In these malignant germ cell tumors, complete resection again constitutes one of the most important prognostic factors. In conclusion, initial incomplete resection at diagnosis should be avoided; if primary resection was incomplete, a second look surgery should be strongly considered. Again, the surgical approach is most often chosen via median sternotomy. Any adjacent organ such as pericardium or thymus should be resected in one piece with the tumor. In some instances, pulmonary wedge resection has to be performed in case of pulmonary metastases or pulmonary infiltration per continuitatem. On the other hand, any metastases that show complete clinical, serological (AFP), and radiographic response do not require surgical resection.

A recent COG report has studied the impact of cisplatinum dose escalation in childhood germ cell tumors (Cushing et al. 2004). Indeed, dose escalation was associated with improved outcome, however with intolerable long-term toxicity, in particular severe ototoxicity. Nevertheless, this approach may be individually chosen in patients that are considered unfavorable risk based on clinical assessment or in relapse patients.

In postpubertal malignant nonseminomatous germ cell tumors, standard chemotherapy may not yield sufficient tumor control since with standard regimen, long-term outcome is at 50% (Bokemeyer et al. 2002; Ganjoo et al. 2000). Therefore, therapy intensification strategies, e.g., with escalated doses of ifosfamide and etoposide have been proposed (Bokemeyer et al. 2003; Schmoll et al. 2003). These regimens are associated with considerable toxicity and therefore require autologous stem cell and growth factor support. However, with such strategies, long-term outcome better than 70% have been reported.

In some mixed malignant germ cell tumors with teratoma elements, a specific situation termed *growing teratoma syndrome* may be observed (Logothetis et al. 1982; Afifi et al. 1997). In these patients, the serologic tumor markers show an adequate response to chemotherapy. Nevertheless, the tumor size does not decrease or may even increase. This radiographic tumor progression despite serologic response of the malignant tumor components is explained by the intrinsic resistance of teratomatous tissue to chemotherapy (Mayer et al. 2003). Therefore, continuation or even intensification of chemotherapy is obsolete. Instead, an immediate change of strategy is required, best with a surgical attempt to resect the teratoma. In tumors deemed irresectable, individual reports on alternative, e.g., antiangiogenic or immunomodulatory therapies have been published (Calaminus et al. 2009; Postovsky et al. 2004). These will usually not induce significant tumor response but may rather induce tumor stabilization and in ideal situations, may facilitate tumor resection.

Seminomas constitute a distinct subgroup of malignant germ cell tumors, occurring almost exclusively in male adolescent or adult patients. They are also considered malignant despite the fact that they do not secrete tumor markers. However, seminomas show an exquisite response to chemotherapy (as well as irradiation). Therefore, these tumors are currently treated with three to four cycles of platinum-based three-agent chemotherapy such as PEB, PEI, or JEB. With this standard treatment, the prognosis of these tumors is favorable and exceeds 80% long-term event-free survival. In most patients, residual tumor after chemotherapy is resected. Nevertheless, the therapeutic impact of tumor resection in highly regressive tumors is controversial. In these instances, postchemotherapy PET assessment may assist in decision-making (De et al. 2001). Any PET positive tumors should be

resected irrespective of size. In contrast, PET negative tumors smaller than 1–2 cm can be followed; whereas, larger tumors should also be excised, in particular in order to resect any teratoma component that cannot be distinguished by PET. In irresectable viable seminomas, irradiation constitutes a promising salvage therapy. However, it is not recommended for first-line therapy since the long-term side effects associated with mediastinal irradiations may be significant (Van den Belt-Dusebout et al. 2006).

24.6 Prognosis

More recent pediatric studies reporting outcome specifically for mediastinal subsets of children and adolescents with malignant germ cell tumors treated with platinum-based regimens suggested that although this site is considered less favorable, event-free survival of 57–88% was achieved (Schneider et al. 2000; Mann et al. 2000; Billmire et al. 2001; Cushing et al. 2004). Ability to surgically resect tumor, either at onset or at postinduction surgery, improves overall survival.

Despite this encouraging data in pediatric mediastinal germ cell tumors as a whole cohort, it should always be considered that metastatic mediastinal mixed malignant germ cell tumors in adolescents (i.e., older than 8–10 years at diagnosis) and adults constitute the prognostically most unfavorable subgroup of germ cell tumors, with an overall survival hardly exceeding 50%. Therefore, a more intensive, maybe even experimental approach is required in these patients in order to overcome the intrinsic treatment resistance in these tumors.

References

Afifi HY, Bosl GJ, Burt ME (1997) Mediastinal growing teratoma syndrome. Ann Thorac Surg 64:359–362

Billmire D, Vinocur C, Rescorla F, Colombani P, Cushing B, Hawkins E, London WB, Giller R, Lauer S (2001) Malignant mediastinal germ cell tumors: an intergroup study. J Pediatr Surg 36:18–24

Blohm ME, Vesterling-Hörner D, Calaminus G, Göbel U (1998) Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol 15:135–142

Bokemeyer C, Nichols CR, Droz JP, Schmoll HJ, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Kanz L, Einhorn L, Hartmann JT (2002) Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol 20:1864–1873

Bokemeyer C, Schleucher N, Metzner B, Thomas M, Rick O, Schmoll HJ, Kollmannsberger C, Boehlke I, Kanz L, Hartmann JT (2003) First-line sequential high-dose VIP chemotherapy with autologous transplantation for patients with primary mediastinal nonseminomatous germ cell tumours: a prospective trial. Br J Cancer 89:29–35

Bussey KJ, Lawce HJ, Himoe E, Shu XO, Heerema NA, Perlman EJ, Olson SB, Magenis RE (2001) SNRPN methylation patterns in germ cell tumors as a reflection of primordial germ cell development. Genes Chromosomes Cancer 32:342–352

Calaminus G, Schneider DT, Weissbach L, Schönberger S, Okpanyi V, Leuschner I, Poremba C, Göbel U (2009) Survival after an antiangiogenetic therapy and surgery in a wide spread growing teratoma originating from a testicular mixed malignant germ cell tumor. Klin Padiatr 221:136–140

Chaganti RS, Houldsworth J (1998) The cytogenetic theory of the pathogenesis of human adult male germ cell tumors. APMIS 106:80–83; discussion 83–84

Chaganti RS, Ladanyi M, Samaniego F, Offit K, Reuter VE, Jhanwar SC, Bosl GJ (1989) Leukemic differentiation of a mediastinal germ cell tumor. Genes Chromosomes Cancer 1:83–87

Cushing B, Giller R, Cullen JW, Marina NM, Lauer SJ, Olson TA, Rogers PC, Colombani P, Rescorla F, Billmire DF, Vinocur CD, Hawkins EP, Davis MM, Perlman EJ, London WB, Castleberry RP (2004) Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study – Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22:2691–2700

De SM, Bokemeyer C, Becherer A, Stoiber F, Oechsle K, Kletter K, Dohmen BM, Dittrich C, Pont J (2001) Predictive impact of 2-18fluoro-2-deoxy-D-glucose positron emission tomography for residual postchemotherapy masses in patients with bulky seminoma. J Clin Oncol 19:3740–3744

Donadio AC, Motzer RJ, Bajorin DF, Kantoff PW, Sheinfeld J, Houldsworth J, Chaganti RSK, Bosl GJ (2003) Chemotherapy for teratoma with malignant transformation. J Clin Oncol 21:4285–4291

Fizazi K, Culine S, Droz JP, Kramar A, Theodore C, Ruffie P, Le CT (1998) Primary mediastinal nonseminomatous germ cell tumors: results of modern therapy including cisplatin-based chemotherapy. J Clin Oncol 16:725–732

Frazier AL, Rumcheva P, Olson T, Giller R, Cushing B, Cullen J, Marina N, London WB (2008) Application of the adult international germ cell classification system to pediatric malignant non-seminomatous germ cell tumors: a report from the Children's Oncology Group. Pediatr Blood Cancer 50:746–751

Ganjoo KN, Rieger KM, Kesler KA, Sharma M, Heilman DK, Einhorn LH (2000) Results of modern therapy for patients with mediastinal nonseminomatous germ cell tumors. Cancer 88:1051–1056

Gobbi D, Rubino M, Chiandetti L, Zanon GF, Cecchetto G (2007) Neonatal intrapericardial teratoma: a challenge for the pediatric surgeon. J Pediatr Surg 42:E3–E6

Göbel U, Schneider DT, Teske C, Schönberger S, Calaminus G (2010) Brain metastases in children and adolescents with extracranial germ cell tumor - data of the MAHO/MAKEI-registry. Klin Pädiatr 222:140–144

Goel D, Prayaga AK, Sundaram C, Raghunadharao D, Rajappa SJ, Rammurti S, Rao TM, Kumar RV (2008) Utility of fine needle aspiration cytology in mediastinal lesions: a clinicopathologic study of 1617 cases from a single institution. Acta Cytol 52:404–411

Grosfeld JL, Skinner MA, Rescorla FJ, West KW, Scherer LR III (1994) Mediastinal tumors in children: experience with 196 cases. Ann Surg Oncol 1:121–127

Group, IGCCC (1997) International Germ Cell Consensus Classification: a prognostic factor- based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 15:594–603

Hainsworth JD (2002) Diagnosis, staging, and clinical characteristics of the patient with mediastinal germ cell carcinoma. Chest Surg Clin N Am 12:665–672

Hartmann JT, Nichols CR, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Fizazi K, Einhorn L, Kanz L, Bokemeyer C (2000) Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. J Natl Cancer Inst 92:54–61

Kaplan SS, Bornstein SG, Christopherson WA, Surti U (1991) Associated leukemia and mixed germ cell tumor in a patient with gonadal dysgenesis. Int J Gynaecol Obstet 35:83–88

Koo CH, Reifel J, Kogut N, Cove JK, Rappaport H (1992) True histiocytic malignancy associated with a malignant teratoma in a patient with 46XY gonadal dysgenesis. Am J Surg Pathol 16:175–183

Logothetis CJ, Samuels ML, Trindade A, Johnson DE (1982) The growing teratoma syndrome. Cancer 50:1629–1635

Mann JR, Raafat F, Robinson K, Imeson J, Gornall P, Sokal M, Gray E, McKeever P, Hale J, Bailey S, Oakhill A (2000) The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18:3809–3818

Mayer F, Stoop H, Scheffer GL, Scheper R, Oosterhuis JW, Looijenga LH, Bokemeyer C (2003) Molecular determinants of treatment response in human germ cell tumors. Clin Cancer Res 9:767–773

Motzer RJ, Amsterdam A, Prieto V, Sheinfeld J, Murty VV, Mazumdar M, Bosl GJ, Chaganti RS, Reuter VE (1998) Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. J Urol 159:133–138

Nichols CR, Heerema NA, Palmer C, Loehrer PJ Sr, Williams SD, Einhorn LH (1987) Klinefelter's syndrome associated with mediastinal germ cell neoplasms. J Clin Oncol 5:1290–1294

Nichols CR, Roth BJ, Heerema N, Griep J, Tricot G (1990) Hematologic neoplasia associated with primary mediastinal germ- cell tumors. N Engl J Med 322:1425–1429

Olak J (1996) Parasternal mediastinotomy (Chamberlain procedure). Chest Surg Clin N Am 6:31–40

Oosterhuis JW, Van den Berg E, de Jong B, Timens W, Castedo SM, Rammeloo RH, Sleijfer DT (1991) Mediastinal germ cell tumor with secondary nongerm cell malignancy, and extensive hematopoietic activity. Pathology, DNA-ploidy, and karyotyping. Cancer Genet Cytogenet 54:183–195

Orazi A, Neiman RS, Ulbright TM, Heerema NA, John K, Nichols CR (1993) Hematopoietic precursor cells within the yolk sac tumor component are the source of secondary hematopoietic malignancies in patients with mediastinal germ cell tumors. Cancer 71:3873–3881

Postovsky S, Epelbaum M, Ben Itzhak O, Beck D, Ben Arush MW (2004) Growing teratoma syndrome treated by interferon alpha-2beta: case report and literature review. Pediatr Hematol Oncol 21:9–16

Priola SM, Priola AM, Cardinale L, Perotto F, Fava C (2006) The anterior mediastinum: anatomy and imaging procedures. Radiol Med 111:295–311

Schmoll HJ, Kollmannsberger C, Metzner B, Hartmann JT, Schleucher N, Schoffski P, Schleicher J, Rick O, Beyer J, Hossfeld D, Kanz L, Berdel WE, Andreesen R, Bokemeyer C (2003) Long-term results of first-line sequential high-dose etoposide, ifosfamide, and cisplatin chemotherapy plus autologous stem cell support for patients with advanced metastatic germ cell cancer: an extended phase I/II study of the German Testicular Cancer Study Group. J Clin Oncol 21:4083–4091

Schneider DT, Calaminus G, Reinhard H, Gutjahr P, Kremens B, Harms D, Göbel U (2000) Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. J Clin Oncol 18:832–839

Schneider DT, Calaminus G, Göbel U (2001a) Diagnostic value of alpha_1_-fetoprotein and human chorionic gonadotropic hormone in infancy and childhood. Pediatr Hematol Oncol 18:11–26

Schneider DT, Schuster AE, Fritsch MK, Hu J, Olson T, Lauer S, Göbel U, Perlman EJ (2001b) Multipoint imprinting analysis indicates a common precursor cell for gonadal and nongonadal pediatric germ cell tumors. Cancer Res 61:7268–7276

Schneider DT, Perlman EJ, Harms D, Fritsch MK, Calaminus G, Göbel U (2002a) Mediastinal germ cell tumors (MGCT) in children and adolescents: age correlates with histological differentiation, genetic profiles and clinical outcome. In: Harnden P, Joffe JK, Jones WG (eds) Germ cell tumours V(26). Springer, London, pp 127–128

Schneider DT, Schuster AE, Fritsch MK, Calaminus G, Göbel U, Harms D, Lauer S, Olson T, Perlman EJ (2002b) Genetic analysis of mediastinal nonseminomatous germ cell tumors in children and adolescents. Genes Chromosomes Cancer 34:115–125

Schneider DT, Calaminus G, Koch S, Teske C, Schmidt P, Haas RJ, Harms D, Göbel U (2004) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42:169–175

Shamberger RC, Holzman RS, Griscom NT, Tarbell NJ, Weinstein HJ (1991) CT quantitation of tracheal cross-sectional area as a guide to the surgical and anesthetic management of children with anterior mediastinal masses. J Pediatr Surg 26:138–142

Sievers S, Alemazkour K, Zahn S, Perlman EJ, Gillis AJ, Looijenga L, Göbel U, Schneider DT (2005) IGF2/H19 imprinting analysis with the methylation-sensitive single nucleotide primer extension method in human germ cell tumors reflects their origin from different stages of primordial germ cell development. Genes Chromosomes Cancer 44:256–264

Van den Belt-Dusebout AW, Nuver J, de Wit R, Gietema JA, ten Bokkel Huinink WW, Rodrigus PTR, Schimmel EC, Aleman BMP, van Leeuwen FE (2006) Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 24:467–475

Pleuropulmonary Blastoma

25

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Contents

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25.1 Background

Pleuropulmonary blastoma (PPB) is a malignant sarcoma of lung and pleura in children under age 6 years. PPB is in the family of dysembryonic developmental tumors of early childhood such as WT (nephroblastoma), embryonal rhabdomyosarcoma (ERMS), neuroblastoma, medulloblastoma, retinoblastoma (Rb), and others. Histopathologically, PPB recapitulates primitive pleuropulmonary mesenchyme from which it is thought to arise (Dehner 1994; Manivel et al. 1988). Because of its rarity, PPB was recognized as a diagnostic entity only in the 1980s (Dehner 1994; Manivel et al. 1987, 1988). In contrast to ~500 Wilms tumors (WT) occurring each year in the United States, 25–50 PPBs are estimated to occur annually.

Despite its rarity, PPB is particularly important among the developmental tumors of childhood for three reasons: first, PPB has a unique, age-related spectrum of presentations and pathology from birth to age 72 months (Dehner 1994; Manivel et al. 1988; Priest et al. 1997, 2009). Second, PPB (OMIM #601200) is a strong marker for familial dysplastic and neoplastic disease in the PPB family tumor and dysplasia syndrome (PPB-FTDS) (Priest et al. 1996, 2009). Finally, the underlying genetic basis of most PPB and PPB-FTDS is mutations in the critical gene *DICER1*, which participates in the highly conserved RNA interference mechanism for posttranscriptional gene silencing (Hill et al. 2009; Seitz 2010). The disease spectrum of the PPB-FTDS, discussed below, appears to result from dysregulated gene silencing as a novel mechanism of childhood dysplasia and neoplasia.

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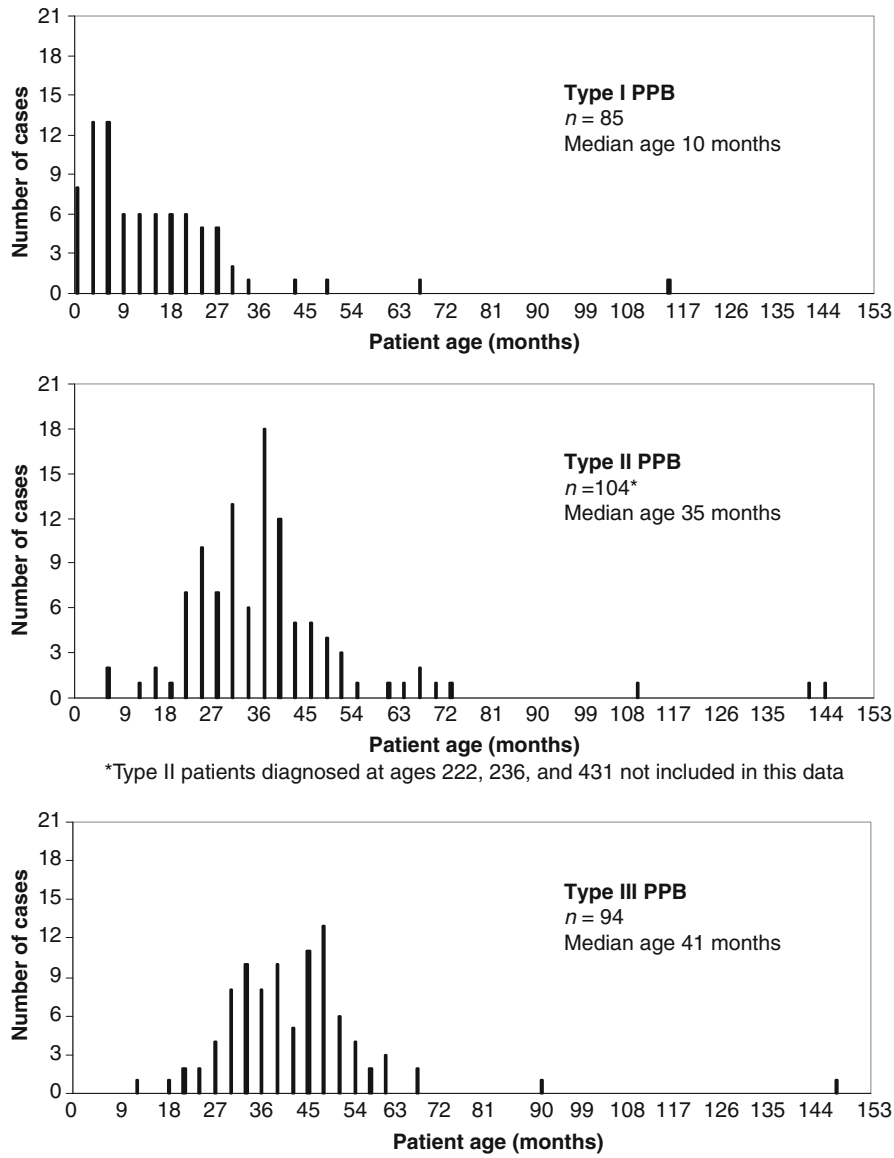

Fig. 25.1 Ages at diagnosis for 283 centrally reviewed patients with types I, II, and III PPB accessioned to the International Pleuropulmonary Blastoma Registry

25.2 Manifestations of PPB

PPB is classified into three interrelated clinicopathologic entities occurring from birth to age 6 years; 96% of PPBs are diagnosed by age 72 months (Fig. 25.1).

The three PPB types are based on gross pathologic morphology augmented by radiographic and microscopic evidence (Dehner 1994; Hill et al. 2008). Type I PPB is the earliest stage of tumorigenesis, may be recognized in prenatal ultrasonography (Miniati et al. 2006) and typically occurs in infancy (Fig. 25.1) (Hill et al. 2008; Priest et al. 2006). Radiographically and grossly, type I PPB is a relatively innocuous-appearing air-filled multilocular cyst in the peripheral lung parenchyma (Fig. 25.2). Until examined pathologically, type I PPB is usually considered as a congenital pulmonary airway malformation (CPAM) (Priest et al. 2009; Stocker 2002). Only rarely are type I cysts fluid filled or infected. Beneath a benign respiratory epithelium, cyst walls and septa contain a scattered, sometimes sparse, population of malignant small cells, suggesting a rhabdomyomatous lineage (Hill et al. 2008).

Type II PPB occurs generally in 1–3 year olds (Fig. 25.1) and has both type I cysts or cyst remnants and grossly visible thickened cyst walls or septa, solid mural nodules or larger tumor excrescences (Fig. 25.3).

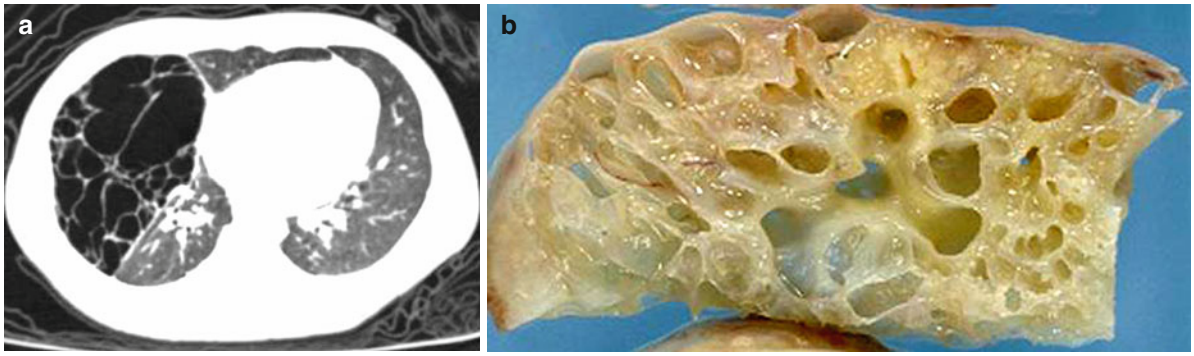

Fig. 25.2 Examples of type I PPB (different patients shown). (**a**)Axial chest CT image. Characteristic of multiloculated, air-filled cyst. CCAM may be radiographically identical. (**b**) Gross pathology (Photograph courtesy of Adrian Charles, M.D., Princess Margaret Hospital, Perth, Australia)

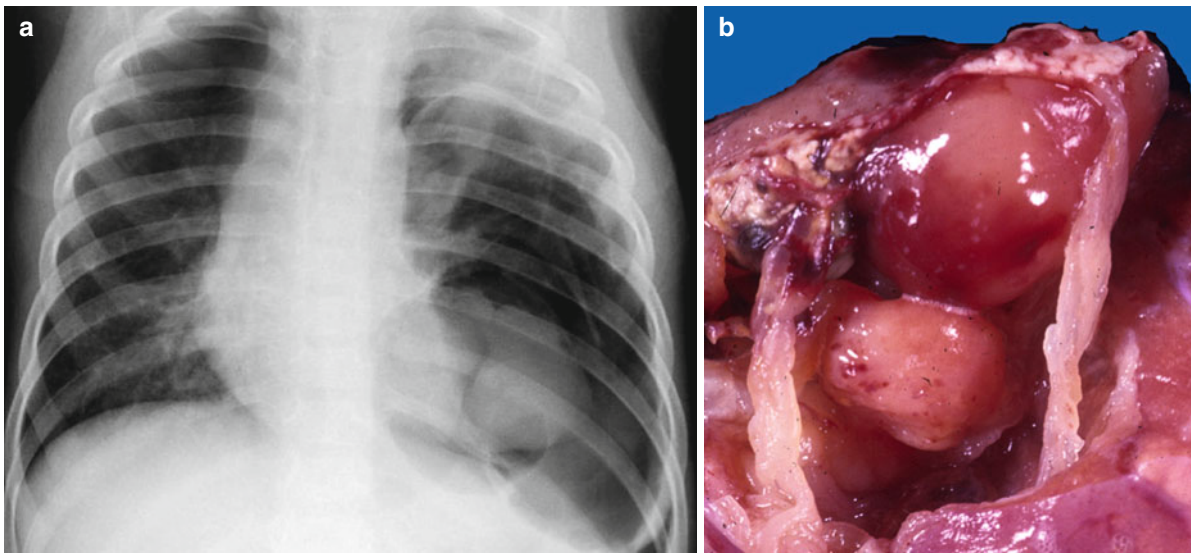

Fig. 25.3 Examples of type II PPB (different patients shown). (**a**) Chest radiograph showing solid nodules within large air-filled cyst in left hemithorax. (**b**) Gross pathology showing polypoid nodules of sarcoma botryoides inside opened pulmonary cyst (Photograph courtesy of David Kelly, M.D., Children's Health System, Birmingham, AL, USA)

The solid tumefactions result from sarcomatous expansion of the subepithelial malignant cells of type I PPB with overgrowth of cyst walls and septa. The solid portions clearly reveal a mixed pattern sarcoma, described below.

Type III PPB (Fig. 25.4a) is a completely solid mixed-pattern sarcoma, described below.

Clear examples of lung cysts progressing over 6–24 months to types II and III PPB are known; such cysts must represent unrecognized type I PPB. Similarly, recurrences of type I PPB are characteristically type II or III disease (Priest et al. 2006). It is not known what proportion of types II and III PPB is preceded by purely cystic type I PPB.

In addition to *progression* of PPB types over the first 6 years of life, type I PPB may *regress* and persist without malignant potential. The residual characteristic of multiloculated cyst, termed type Ir (regressed) PPB, may be diagnosed at any age; the radiographic appearance is that of type I PPB (Fig. 25.2a). Type Ir PPB may be multiple or bilateral and is typically small (<2–3 cm diameter) but may occupy up to approximately 30% of the hemithorax. Type Ir PPB is most often recognized in relatives of PPB patients

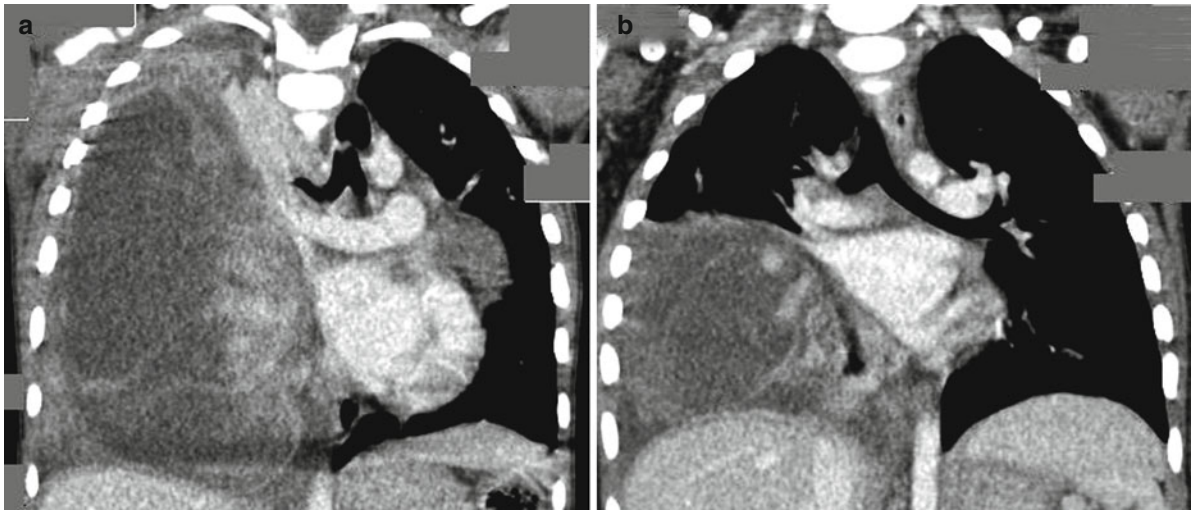

Fig. 25.4 Example of extensive type III PPB in a 33-month-old child. (**a**) Coronal CT image at carina, at diagnosis. (**b**) CT image 12 weeks later following four courses of IVADo chemotherapy. This tumor arose in parietal pleura, and resection did not involve lobectomy. This patient had no evidence of disease 15 months from diagnosis

(Priest et al. 2009; Hill et al. 2008), just as retinocytoma is an occult manifestation of predisposition in hereditary Rb families (Dimaras et al. 2008). Regression of type II or III PPB has not been observed.

Type I PPB presents with respiratory difficulty from a large cyst or pneumothorax or as an incidental finding on chest radiograph or prenatal ultrasound (Priest et al. 1997, 2009; Miniati et al. 2006). Pneumothorax, including tension pneumothorax, suggests PPB and is not common in CPAM (Priest et al. 2009; Stocker 2002). Type II PPB may also present with pneumothorax, but typically types II and III PPB present with cough, mild to severe respiratory distress, and nonspecific symptoms such as fever, malaise, and anorexia. Types II and III PPB are often diagnosed as "pneumonia"; after failure to improve, investigations reveal tumor. Type III PPB, and occasionally type II PPB, often occupies an entire hemithorax (Fig. 25.4a). Types II and III PPB may extend into venous and arterial great vessels, leading to vascular symptoms and systemic embolism (Priest et al. 2011a). Type Ir PPB may present with pneumothorax but is most often occult and discovered incidentally on chest computed tomography (CT) during the work-up of another disease or when surveying PPB relatives for disease.

Types II and III PPB may metastasize (not observed in type I PPB) most frequently to cerebral parenchyma, estimated to occur in 11% and 55%, respectively, of types II and III PPB cases; the chest is free of disease in 50% of cerebral metastasis cases (Priest et al. 2007). Cerebrospinal fluid dissemination occurs virtually only after prolonged cerebral disease; cytology is rarely positive. Other metastatic sites include the pleural space, lung parenchyma, bones, and liver. Marrow disease is known in only one of 500–600 described cases. Pleural effusion is moderately common in types II and III PPB, but cytology is rarely positive. Thoracic lymph node infiltration is very rare. Bone and brain metastases may be present at diagnosis; metastases and recurrences occur from diagnosis to approximately 36 months later.

25.3 Pathology Overview

At gross examination, types I and Ir PPB may appear unicystic or multicystic; however, at low magnification, both demonstrate a multilocular architecture with delicate septa which are characteristic and suggest the PPB diagnosis (Hill et al. 2008). In type I PPB, a population of small primitive mesenchymal cells is found in the stroma beneath a benign respiratory epithelial lining; these cells may be a localized single focus, several foci or a diffuse proliferation, resembling the cambium layer effect of a sarcoma botryoides. The primitive small cells may display rhabdomyoblastic differentiation, and prominent eosinophilic cytoplasm may be present. The presence of rhabdomyoblasts is not

necessary for the pathologic diagnosis. Small nodules of immature cartilage are often found in the septa and are not necessarily accompanied by the small primitive cells. Because the small primitive cells or nodules of cartilage may be exquisitely focal, it may be necessary to submit an entire cyst specimen for microscopic examination. In type Ir PPB, the small cell population is not seen; there may be evidence of necrotic or hyalinized cyst walls and septa and hemosiderin-laden macrophages.

Type II PPB retains evidence of type I cysts but grossly demonstrates areas of solid tumor. The evidence for residual cysts may be clinical (pneumothorax), radiographic or pathologic. Type III PPB is completely solid. Elsewhere in the lungs, types II and III PPB patients may have separate, scattered, typically small Type I or Ir PPB. Microscopically, the solid areas of types II and III PPB reveal an aggressive, primitive mixed-pattern sarcoma: blastema, anaplasia, ERMS, chondrosarcoma, undifferentiated spindle-cell proliferations, necrosis; rarely, other tissue types such as neuroblastoma are present. Anaplasia may be dramatic with frequent bizarre mitotic figures; anaplasia is rare in type I PPB (~6% of cases) but present in 77% and 90%, respectively, of types II and III PPB (Hill et al. 2008). Tumors may be extremely friable with large areas of necrosis; pseudocysts, secondary to necrosis, do not designate type II disease. Small biopsies of large tumors may sample a monomorphic histopathology, typically ERMS; the International PPB Registry does not consider such samples diagnostic of PPB unless a mixed pattern is seen in subsequent resection specimens. Fine needle aspiration cytology is not recommended for diagnosis. Type III PPB may arise in and be entirely pleural based, including tumors of the parietal pleura (Fig. 25.4a). Malignant epithelium is not seen in PPB, differentiating it from "pulmonary blastoma", a biphasic tumor of adulthood, which nevertheless occurs rarely in young children (Dehner 1994).

The differential diagnosis of type I PPB includes CPAM, which is radiographically indistinguishable from type I PPB, a newly recognized fetal lung interstitial tumor (FLIT) (Dishop et al. 2010) and cystic primary pleuropulmonary synovial sarcoma (CPPSS) (Cummings et al. 2010). FLIT is typically seen in newborns; although the histology may be reminiscent of type I PPB, the radiographic appearance of an airless opaque mass is typical of FLIT and unlike type I PPB. Although CPPSS may present with pneumothorax (Belcher et al. 2007), it is a disease of teen and young adult years during which type I PPB is extraordinarily unlikely (Cummings et al. 2010). A subtle spindle-cell population in cyst walls and septa suggests type I PPB; gene fusion markers for synovial sarcoma are useful (Cummings et al. 2010).

The differential diagnosis of solid PPB includes "monomorphic" pulmonary ERMS, biphasic adult-type pulmonary blastoma, and monomorphic spindle-cell proliferations, such as monomorphic pulmonary synovial sarcoma in teens.

25.4 PPB Treatment

No prospective treatment trials for any PPB type have been done because of the disease's rarity.

Surgical extirpation is the primary treatment for type I PPB. Type I PPB may be exophytic and readily removed at a stalk, or it may deeply replace and distort one or more lobes, requiring lobectomy. Wedge resections suffice for intermediate disease. No case is described where unilateral pneumonectomy was necessary for type I PPB. Some type I PPBs are widely multifocal (unilateral or bilateral); surgical removal is not possible; the largest lesion(s) should be removed for pathologic examination and further treatment based on pathologic findings. A patient may have both types I and Ir cysts. Postoperative i.e. chemotherapy scan is recommended to determine whether residual cysts remain, which may have been compressed and undetected initially. For type I PPB, adjunctive chemotherapy may be useful (vincristine (V), dactinomycin (A), and cyclophosphamide (C)) (Priest et al. 2006). Among approximately 100 registry type I PPB patients, only one is known who received adjuvant chemotherapy and then had recurrence; however, many type I patients have been cured with surgery alone (Priest et al. 2006). No chemotherapy is recommended for patients with only type Ir PPB.

Types II and III PPB require multimodal therapy. These tumors often occupy >50% of a hemithorax (Fig. 25.4a); surgeons may prefer biopsy to resection. Core needle biopsies may not sample diverse histologic subtypes but will probably yield a "sarcoma" diagnosis, allowing selection of neoadjuvant chemotherapy. Multiple core needle biopsies or open excisional biopsy are recommended. Large tumors are sometimes resected and may be encapsulated or conversely extremely

friable with pre- or intraoperative rupture, gross pleural spillage, and piecemeal resection.

Types II and III PPB are aggressive sarcomas, and chemotherapy recommendations are the same for both types. Adjuvant and neoadjuvant regimens typically follow aggressive sarcoma therapies. In Europe, "VAIAd" (courses of V, A, and ifosfamide (I) alternating with V, doxorubicin (Ad), and I) is used for PPB (Kirsch et al. 2005; Indolfi et al. 2007). Regimens including platinum compounds, etoposide, or other anthracyclines are generally no longer used in Europe. In the United States, VAC, VACAd, and VAC alternating with Ad-cisplatin have been used most often. Since 2007, the International PPB Registry has recommended "IVADo" (Do, doxorubicin), four courses at 3-week intervals, followed by IVA continuation therapy. IVADo employs four agents together for maximal early effect, especially for neoadjuvant use. Neoadjuvant responses range from approximately 40 to 90+% three-dimensional volume reduction during 16 weeks of IVADo (Fig. 25.4b). PPB cannot be controlled only by chemotherapy, and surgical resection at week 12 or 16 must be considered. Aggressive resections, including extrapleural pneumonectomy for an extensively involved hemithorax, may be appropriate. Diaphragmatic resections and more rarely small chest wall resections have been done. Children appear to tolerate well lobectomy or pneumonectomy, although no long term studies of PPB survivors have been done.

Adjunctive radiation therapy may be considered for focal sites of known residual. No study has focused specifically on PPB outcome vis-à-vis radiotherapy usage. Sarcoma doses seem necessary; mediastinal disease margins may be troublesome because of anthracycline use. Whole-lung radiation at lung tolerance doses would seem not to be useful but has not been formally evaluated.

Treatments for PPB recurrences are highly varied. Thoracic recurrence therapy is likely to include surgery, relapse sarcoma regimens, or new agents, with or without focal radiation. A small proportion of children with recurrent chest disease survive. For responsive disease or "consolidation" of a disease-free condition, high-dose chemotherapy with autologous stem-cell reconstitution has been used for several PPB patients who have survived.

Cerebral metastases can be cured with excellent outcomes (Priest et al. 2007); perhaps 10–20% of children with cerebral metastases survive (unpublished International PPB Registry observation). General guidelines include neurosurgical resection followed by radiotherapy, which may include high-dose short-course focal therapy ("gamma knife") protocols. If a cerebral metastasis occurs during chemotherapy, one could consider interdigitating an ifosphamide, carboplatinum, etoposide regimen, found useful in treating cerebral metastases of clear cell sarcoma of kidney (Radulescu et al. 2008), with the original chemotherapy regimen. Some brain metastases have been cured with surgery and radiation (Priest et al. 2007).

25.5 Prognosis

Figure 25.5 presents survival data by PPB type for 295 registry-confirmed patients treated heterogeneously at institutions around the world, comparing diagnoses before and after the year 2000. In general, it appears as if rates of survival are somewhat improved for more recent diagnoses; reasons for this are not known. Overall survivals are approximately 90% for type I PPB and 40–60% for types II and III PPB.

25.6 *DICER1* Mutations and the PPB Family Tumor and Dysplasia Syndrome (PPB-FTDS)

In 2009, germline mutations were described in PPB patients from families exhibiting PPB, lung cysts, CN, and ERMS (Hill et al. 2009). Subsequently, *DICER1* mutations have been described in 50–70% of PPB patients and in many associated diseases in the PPB family tumor and dysplasia syndrome (Table 25.1) (Hill et al. 2010; Slade et al. 2011; Bahubeshi et al. 2010; Rio Frio et al. 2011; Priest et al. 2011b). PPB-FTDS affects 33% of families in which PPB is diagnosed, making PPB one of the strongest markers among pediatric malignancies for syndromic/familial disease (Plon and Malkin 2005; Scott et al. 2006). The PPB-FTDS phenotype is unique and has highly variable expressivity,

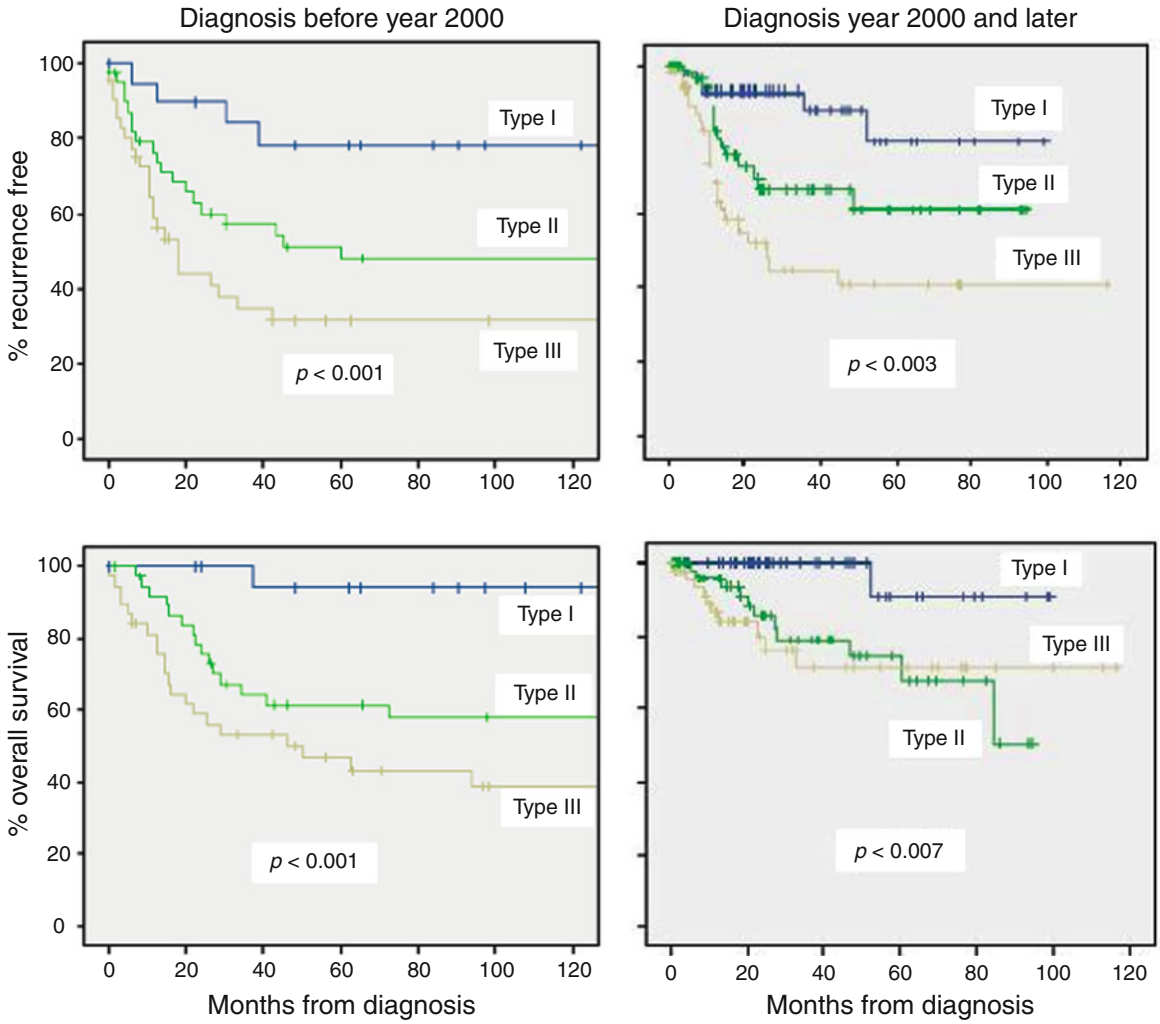

Fig. 25.5 Life-table recurrence-free and overall survival by PPB type in 100 patients diagnosed prior to year 2000 and 180 patients diagnosed in year 2000 and later (based on diagnosis date for International PPB Registry enrollees consecutively accessioned when pathologic diagnosis is centrally confirmed). Log rank *p* values shown

autosomal dominant inheritance, many unaffected carriers, multifocal and bilateral disease, young age at diagnosis for certain phenotypic conditions compared to their sporadic counterparts and affects individuals predominantly under age 20 years. Both PPB and the PPB-FTDS also occur without *DICER1* mutation.

25.7 Disease Screening and Genetic Counseling

Given the pleiotropy, varied expressivity, and relatively low disease penetrance in the PPB-FTDS, clinical screening recommendations are complex.

Table 25.1 Conditions in the pleuropulmonary blastoma family tumor and dysplasia syndrome (PPB-FTDS)

Condition	Characteristic PPB-FTDS condition	*DICER1* mutation reported
Pleuropulmonary blastoma[a,b]	Yes	Hill et al. (2009, 2010)
Lung cysts[a,b]	Yes	Hill et al. (2009, 2010), Bahubeshi et al. (2010)
Cystic nephroma[a,b]	Yes	Hill et al. (2009), Slade et al. (2011), Bahubeshi et al. (2010)
Rhabdomyosarcoma (including bladder rhabdomyosarcoma)		Hill et al. (2009), Rio Frio et al. (2011), Unpublished
Nodular thyroid hyperplasia[a,b] (multinodular goiter)		Slade et al. (2011), Rio Frio et al. (2011)
Differentiated thyroid cancer		
Nasal chondromesenchymal hamartoma	Yes	Unpublished
Ciliary body medulloepithelioma (diktyoma)	Yes	Slade et al. (2011)
Ovarian sex cord stromal tumors[a,b] (especially Sertoli–Leydig cell tumors)	Yes	Slade et al. (2011), Rio Frio et al. (2011)
Uterine cervix sarcoma botryoides (ERMS)[a]	Yes	(Unpublished)
Hamartomatous intestinal polyps		(Unpublished)
Wilms tumor		Slade et al. (2011)
Seminoma		Slade et al. (2011)
Childhood cancers: sarcomas and other dysembryonic tumors, including neuroblastoma and perhaps leukemia		
Medulloblastoma		Slade et al. (2011)

[a]Familial
[b]Bilateral examples reported with other PPB-FTDS conditions

Diseases may occur in many organs (Table 25.1) over the first two decades of life. PPB is the most frequent manifestation of the FTDS. Because type I PPB is highly curable and may evolve into advanced types II and III PPB with a much less favorable outlook (Fig. 25.5), identifying individuals genetically at risk and detecting and eradicating type I PPB by 8–12 months of age are the rational goals for any screening program.

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References

Bahubeshi A, Bal N, Rio Frio T et al (2010) Germline *DICER1* mutations and familial cystic nephroma. J Med Genet 47:863–866

Belcher E, Lawson MH, Nicholson AG, Davison A, Goldstraw P (2007) Congenital cystic adenomatoid malformation presenting as in-flight systemic air embolisation. Eur Respir J 30:801–804

Cummings NM, Desai S, Thway K et al (2010) Cystic primary pulmonary synovial sarcoma presenting as recurrent pneumothorax: report of 4 cases. Am J Surg Pathol 34:1176–1179

Dehner LP (1994) Pleuropulmonary blastoma is the pulmonary blastoma of childhood. Semin Diagn Pathol 11:144–151

Dimaras H, Khetan V, Halliday W et al (2008) Loss of RB1 induces non-proliferative retinoma: increasing genomic instability correlates with progression to retinoblastoma. Hum Mol Genet 17:1363–1372

Dishop MK, McKay EM, Kreiger PA et al (2010) Fetal Lung Interstitial Tumor (FLIT): a proposed newly recognized lung tumor of infancy to be differentiated from cystic pleuropulmonary blastoma and other developmental pulmonary lesions. Am J Surg Pathol 34:1762–1772

Hill DA, Jarzembowski JA, Priest JR, Williams G, Schoettler P, Dehner LP (2008) Type I pleuropulmonary blastoma: pathology and biology study of 51 cases from the international pleuropulmonary blastoma registry. Am J Surg Pathol 32:282–295

Hill DA, Ivanovich J, Priest JR et al (2009) *DICER1* mutations in familial pleuropulmonary blastoma. Science 325:965

Hill DA, Wang JD, Schoettler P et al (2010) Germline *DICER1* mutations are common in both hereditary and presumed sporadic pleuropulmonary blastoma [abstract]. Lab Invest 90:311

Indolfi P, Bisogno G, Casale F et al (2007) Prognostic factors in pleuro-pulmonary blastoma. Pediatr Blood Cancer 48:318–323

Kirsch S, Leuschner I, Int-Veen C et al (2005) Sixteen children with pleuropulmonary blastoma – results of the German Cooperative Soft Tissue Sarcoma Group [abstract]. Sarcoma 9:88

Manivel C, Wick M, Dehner L (1987) Thoracopulmonary blastoma – reassessment of an embryonal neoplasm. Lab Invest 56:48

Manivel JC, Priest JR, Watterson J et al (1988) Pleuropulmonary blastoma. The so-called pulmonary blastoma of childhood. Cancer 62:1516–1526

Miniati DN, Chintagumpala M, Langston C et al (2006) Prenatal presentation and outcome of children with pleuropulmonary blastoma. J Pediatr Surg 41:66–71

Plon SE, Malkin D (2005) Childhood cancer and heredity. In: Pizzo PA (ed) Principles and practice of pediatric oncology, vol 5. Lippincott Williams & Wilkins, Philadelphia, pp 14–37

Priest JR, Watterson J, Strong L et al (1996) Pleuropulmonary blastoma: a marker for familial disease. J Pediatr 128:220–224

Priest JR, McDermott MB, Bhatia S, Watterson J, Manivel JC, Dehner LP (1997) Pleuropulmonary blastoma: a clinicopathologic study of 50 cases. Cancer 80:147–161

Priest JR, Hill DA, Williams GM et al (2006) Type I pleuropulmonary blastoma: a report from the International Pleuropulmonary Blastoma Registry. J Clin Oncol 24:4492–4498

Priest JR, Magnuson J, Williams GM et al (2007) Cerebral metastasis and other central nervous system complications of pleuropulmonary blastoma. Pediatr Blood Cancer 49:266–273

Priest JR, Williams GM, Hill DA, Dehner LP, Jaffe A (2009) Pulmonary cysts in early childhood and the risk of malignancy. Pediatr Pulmonol 44:14–30

Priest JR, Andic D, Arbuckle S, Gonzalez-Gomez I, Hill DA, Williams G (2011a) Great vessel/cardiac extension and tumor embolism in pleuropulmonary blastoma: a report from the International Pleuropulmonary Blastoma Registry. Pediatr Blood Cancer 56(4):604–609

Priest JR, Williams GM, Manera R et al (2011b) Ciliary body medulloepithelioma: four cases associated with pleuropulmonary blastoma–a report from the International Pleuropulmonary Blastoma Registry. Br J Ophthalmol 95(7):1001–1005

Radulescu VC, Gerrard M, Moertel C et al (2008) Treatment of recurrent clear cell sarcoma of the kidney with brain metastasis. Pediatr Blood Cancer 50:246–249

Rio Frio T, Bahubeshi A, Kanellopoulou C et al (2011) DICER1 mutations in familial multinodular goiter with and without ovarian sertoli-leydig cell tumors. JAMA 305:68–77

Scott RH, Stiller CA, Walker L, Rahman N (2006) Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. J Med Genet 43:705–715

Seitz H (2010) siRNAs: the hidden face of the small RNA world. Curr Biol 20:R108–R110

Slade I, Bacchelli C, Davies H et al (2011) DICER1 syndrome – clarifying the diagnosis, clinical features and management implications of a pleiotropic tumor predisposition syndrome. J Med Genet 48(4):273–278

Stocker JT (2002) Congenital pulmonary airway malformation – a new name for and an expanded classification of congenital cystic adenomatoid malformation of the lung. Histopathology 41:424–431

Bronchial Carcinoids and Carcinomas

26

Michael Semik, Antje Redlich, and Peter Vorwerk

Contents

26.1 Introduction

Despite their considerable organ size, the lungs rarely give rise to malignant tumors during childhood and adolescence. If they do, these tumors may present with embryonal structures resembling immature stages of pulmonary development (pleuropulmonary blastoma). On the other hand, tumors may present with organ-specific bronchial or neuroendocrine differentiation, while classic adeno-, squamous cell, or small cell carcinomas are exceedingly rare.

Bronchial carcinoids are tumors of the neuroendocrine system and account for 80–85% of all primary malignant lung tumors during childhood and adolescence (Christenson et al. 1999). Neuroendocrine tumors are a group of neoplasms that histologically present with uniformly appearing cells that arise from the neuroepithelial cells within the bronchial epithelium. They may differ from each other in their biology, prognosis, and genetics. In the lung, they are called carcinoid, ranging from the low-grade typical carcinoids to the intermediate-grade atypical carcinoids and high-grade small- or large-cell neuroendocrine carcinomas (Klöppel et al. 2007a). The term carcinoid was first introduced in 1907 by Oberndorfer to describe the unique feature of behaving like a benign tumor despite having a malignant appearance (Oberndorfer 1907; Klöppel 2007a, b). Initially, bronchial carcinoids were thought to be benign and therefore classified as bronchial adenomas (Davila et al. 1993). The classification and nomenclature of these tumors has further evolved with the understanding of their biological and clinical behavior (Christenson et al. 1999).

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Primary tumors of the lung are very rare in children, since their incidence rises with age. Most of the reported cases are neuroendocrine tumors of the bronchial system; however, metastasis and benign or reactive lesions are much more frequent in this age group. However, the true incidence is unknown. Cohen and Kaschula (1992) reported about eight patients in a 31-year period in a single center. In Germany, nine children with bronchial carcinoids have been registered in the GPOH-MET study on malignant endocrine tumors over a period of 14 years. Nevertheless, a significant registration gap is assumed.

Bronchial carcinoma (lung cancer) is the most commonly diagnosed cancer worldwide and primarily a disease of older populations, mostly in the sixth and seventh decades of life. It is extremely rare in childhood and adolescence. Within the United States SEER registry from 1992 to 2010 and overall 17,000 children and adolescents with malignant solid tumors, 47 patients – less than 20 years of age – with lung cancer were counted (Lit. US SEER registry, status October 2010), 31 patients in the age group from 15 to 19 years, 13 patients from 10 to 14 years, 2 patients from 5 to 9 years, and 1 patient from 0 to 4 years. In the German Rare Tumor Registry, only one 17-year-old patient has been registered over a 3-year period, illustrating the absolute rarity of this tumor type in children and adolescents.

The low incidence of bronchial carcinoma in young may be explained in the light of the general knowledge that, like almost no other tumor, the development of bronchial carcinoma is tightly correlated to exogenous factor in the background of a genetic susceptibility. Thus, smoking and genetic predisposition were found as risk factors for bronchial carcinoma in young patients (under 45 years), with a predominance of adenocarcinoma (Kreuzer et al. 1998; Ramalingam et al. 1998). Bronchial carcinoma incidence trends follow the trend of prevalence of cigarette smoking, with a latency of approximately 20 years. The results of a segregation analysis suggest genetic contribution to bronchial carcinoma in the very young, particularly in nonsmokers (Kreuzer et al. 1999; Rosenberger et al. 2008).

Overall, data suggest that bronchial carcinoma is not a more aggressive disease in younger patients and that all patients with lung cancer should be managed along the same therapeutic guidelines (Ramalingam et al. 1998; Goeckenjan et al. 2010).

26.2 Clinical Diagnosis, Pretherapeutic Assessment in Lung Tumors, Staging

The detection of malignant lung tumors in children is problematic and difficult. Children most commonly present with unspecific respiratory complaints. Wheezing, lingering cough, pain, hemoptysis, and recurrent pneumonia (in the same lobe) may present characteristic symptoms and may be apparent for up to 1 year before diagnosis. Symptoms may occur as isolated symptoms or in combination (Wang et al. 1993; Rizzardi et al. 2009; Srirajaskanthan et al. 2009). General pediatricians should be aware that wheezing localized to one lung is a characteristic finding not only of lung tumors but also of other reasons of bronchial obstruction and always requires bronchoscopy. Carcinoid tumors or carcinomas can also be found accidentally in X-rays of the chest in asymptomatic patients (Bini et al. 2008). However, of note pediatric patients are rarely asymptomatic. Nevertheless, the possibility of a primary lung tumor is often considered only when radiographic abnormalities or symptoms persist or fail to respond to antibiotic therapy (McCahon 2006).

Neuroendocrine tumors may secrete neuroendocrine peptides, although it is extremely rare for bronchial carcinoids to course a carcinoid syndrome without metastatic spread (Ward et al. 1984). However, the occurrence of Cushing's syndrome due to ectopic ACTH secretion has been reported. Typical bronchial carcinoids are found more frequent than atypical carcinoids, which are bigger in size, more peripherally located, and less favorable (Asamura et al. 2006). Local invasion and metastases are seen in 25% of children (Rizzardi et al. 2009). The propensity of the tumor to metastasize correlates with the histologic grade of atypia. The metastatic pattern includes lymph nodes, liver, and less frequently skeleton, CNS, and adrenal glands (Soga and Yakuwa 1999).

The clinical symptoms of bronchial carcinoma may also vary significantly and are undistinguishable from bronchial carcinoids. Typical pulmonary symptoms are cough, dyspnea, hemoptysis, and postobstructive pneumonia. Because of the aggressive nature of this cancer, two thirds of patients exhibit symptoms from locally advanced or metastatic disease, such as bone pain or head swelling due to vena cava superior occlusion.

Basic preoperative diagnostic work-up is comparable for carcinoids and carcinoma and includes clinical investigation, chest posteroanterior X-ray, CT scan of the

chest Fig. 26.2 and Fig. 26.3, and bronchoscopy with tumor biopsy. Pulmonary function tests should be performed routinely.

In neuroendocrine tumors, octreotide or MIBG scintigraphy can be used to reveal metastasis and to open palliative treatment options. (18)F-DOPA use in PET/CT is the optimal tracer for carcinoids; however, the significance of the method is still under research (Jager et al. 2008; Koopmans et al. 2008).

Primary staging of the bronchial carcinoma patient includes MRI of the brain, CT or ultrasonography of the abdomen, and possibly PET-CT scan (in Germany optional), which verifies metastatic-free or metastatic disease (Table 26.1). In case of bone pain, bone scintigraphy is recommended. Mediastinal lymph node staging is realized by endobronchial and esophageal ultrasound. Complementary cervical mediastinoscopy or video-assisted thoracoscopy can be performed, especially in suspected N2 disease or undefined pleural effusions. The clinical and pathological staging of bronchial carcinoma is based on the TNM system.

Proof of tumor histology – with differentiation of non-small cell bronchial carcinoma vs. small cell bronchial carcinoma – has significant impact on prognosis and treatment protocols. Nowadays analysis of molecular markers as KRAS, EGFR, and ALK mutations can indicate targeted therapies individually.

The pathological examination of the specimens should be performed by an experienced specialist and confirmed by reference pathologists for children. Seventy-five percent of the carcinoids arise from the lobar bronchi, 10% from the mainstream bronchi, and 15% in the lung periphery (Davila et al. 1993). Small biopsies are not representative and can often be misinterpreted (Filosso et al. 2002).

Bronchial carcinoids can occur in 5% of patients with MEN1. Although more prevalent in older patients, an analysis of the menin gene should be performed whenever a suspicion of a genetic background exist (Sachithanandan et al. 2005).

26.3 Treatment

In experienced and skilled hands, conservative procedures are the treatment of choice for the management of pediatric bronchial carcinoids (Rizzardi et al. 2009). Resection is the treatment of choice for carcinoids in adolescents and adults (Detterbeck 2010). Lung-sparing bronchoplastic procedures and limited resections are favorable for central, most typical carcinoids Fig. 26.1. In peripheral carcinoids, wedge resection in the young and lobectomy in the older adult patient is recommended. Lymphadenectomy may be beneficial, especially in N1 or N2 carcinoid tumors. In locally advanced carcinoids with preoperative N1 or N2 disease, mostly atypical carcinoids, neoadjuvant chemotherapy and radiation can be indicated, followed by anatomical resection.

Endobronchial resection of typical carcinoids is possible, but complete resection can be achieved only in half of patients with recurrence in 5%, demanding subsequent surgical resection (Detterbeck 2010). Patient selection for endobronchial removal seems to be essential.

If tumors are widespread metastatic or unresectable, palliative and symptomatic treatment is based on surgical or endobronchial debulking, tumor embolization, and biotherapy with somatostatin analogues. Chemotherapy and radiotherapy are usually ineffective, but novel drugs such as tyrosine kinase receptor inhibitors show promising results in phase II clinical studies (Gustafsson et al. 2008).

Radical resection is a prerequisite of cure in bronchial carcinoma, too. After definition of tumor stage, stage-dependent treatment is indicated in the young as in older subjects, primary surgical in stage I and II vs. multimodal in stage III vs. systemic and palliative in stage IV Fig. 26.4. Anterolateral thoracotomy with

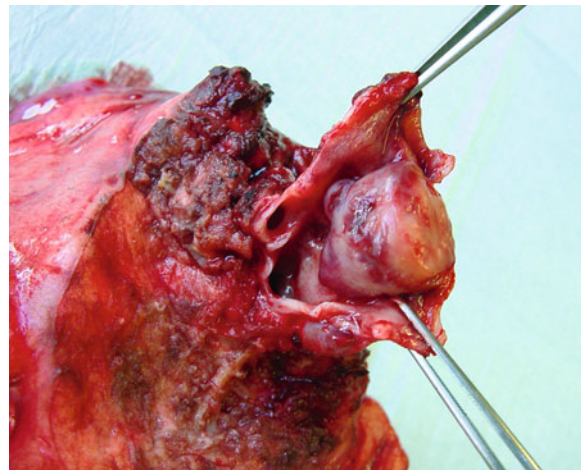

Fig. 26.1 Carcinoid tumor in central upper lobe bronchial after bronchoplastic resection (surgical specimen)

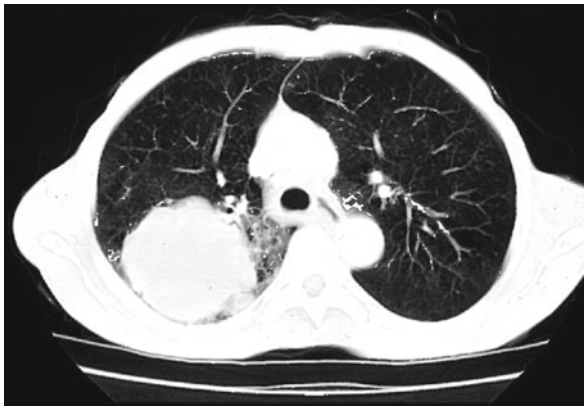

Fig. 26.2 Large lung cancer in right upper lobe (Chest CT-scan)

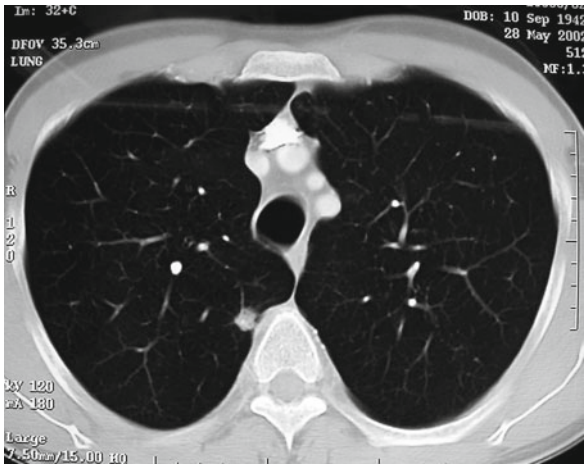

Fig. 26.3 Small lung cancer in right upper lobe (Chest CT-scan)

anatomic lung resection (lobe or more) and lymphadenectomy is therapy of choice with best long-term survival; tumor negative resection margins (R0) are prognostically decisive. In pathologic N1 status (pN1 = stage II), adjuvant chemotherapy (four courses) is state of the art and improves survival (Winton and Livingston (2004). In locally advanced bronchial carcinoma, mainly in stage III, extended (surgical) procedures are indicated; these are bronchoplastic or angioplastic resections; chest wall, intrapericardial, or atrial resections in T4 organ involvement; or other procedures. Stage IIIA is mainly defined by different extent of ipsilateral lymphatic metastases to the mediastinum (N2 disease), which indicate different treatment protocols (Robinson et al. 2007). Incidental N2 disease (postoperative or intraoperative diagnosis of pN2 = stage $IIIA_1$ or $IIIA_2$) receive adjuvant chemotherapy and radiotherapy, sequentially. In preoperatively diagnosed N2 disease (single or several N2 = $IIIA_3$ and multilevel or bulky disease N2 = $IIIA_4$) and amenable resection, patients receive neoadjuvant chemotherapy, surgery, and radiotherapy, sequentially. Patients with tumor regression (CR, PR) or stable disease (SD) and proven resectability are operated on, with the aim of complete resection (R0). All patients with N2 disease receive adjuvant radiotherapy (50 Gy) of primary tumor lesion and mediastinum, the dose is dependent on the pathological resection status (R0 or R1/R2). Patients with tumor progression (PD) or unresectable disease receive definitive radiotherapy or combined radiochemotherapy (N3 disease).

Further adjuvant chemotherapy is chosen individually and can be influenced by the pathological tumor regression (yTNM). In stage IV disease, palliative chemotherapy is state of the art. Additionally, in the young (and selected older patients), targeted therapy can be initiated in EGFR- or ALK-positive tumors, or in second line therapy.

Modern chemotherapy regimen of non-small cell bronchial carcinoma commonly include a platin compound (cis- or carboplatin) in combination with another drug such as gemcitabine, vinorelbine, paclitaxel, etoposide, etc. Compared to single-drug regimen, two-drug combinations are associated with higher toxicity but also a slight survival advantage. However, intensification with three drugs has not shown a significant survival benefit but a significant increase of hematologic toxicity. In bronchial carcinomas with positive EGFR mutation status, targeted therapy with EGFR inhibitors such as erlotinib or gefinitib is recommended (Janne et al. 2010).

For small cell carcinoma, cisplatin is recommended, too. It is most widely applied in combination with etoposide or camptothecins such as topotecan. In this chemosensitive tumor, additional agents such as ifosfamide may yield an additional survival benefit.

26.4 Results and Comment

The prognosis of bronchial neuroendocrine tumors in children is, with 90% overall survival, good (Hartman and Shochat 1983). Typical carcinoid tumors have a

Table 26.1 Diagnostic assessment of bronchial carcinoids and bronchial carcinoma

Procedure	Carcinoid	Carcinoma	Specific questions
Physical examination	+	+	Airway obstruction, lymphatic metastasis, hemoptysis, wheezing, vena cava superior obstruction
Pulmonary function	+	+	Preoperative status
Laboratory assessment			
Clinical Chemistry	+	+	Organ function
ChA, NSE, HIAA(urine)	+		Neuroendocrine tumor origin
ACTH, cortisone	+		Cushing?
Radiographic assessment			
Chest X-ray T	+	+	Staging
Chest CT	+	+	Local stage, lymph nodes
Abdominal ultrasound	+	+	Metastases (especially liver)
PET-CT		+	Local stage, metastases
Brain MRI	(+)	+	Brain metastases
Bone scan	(+)	(+)	Bone metastases
Octreoid scan	+		Metastases, palliative therapeutic option?
Invasive examinations			
Bronchoscopy	+	+	Preoperative staging
Endobronchial US	+	+	Local and nodal stage
Esophageal US	+	+	Local and nodal stage
Pathologic and genetic examination			
MENIN mutation	+		MEN 1?
KRAS, *EGFR*, *ALK*		+	Targeted therapy?

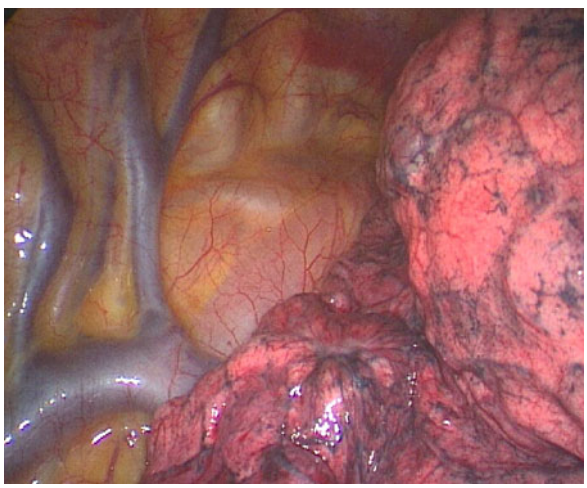

Fig. 26.4 Peripheral bronchial carcinoma in apical segment of right lower lobe (thoracoscopic view)

better outcome than atypical (60–70%) (Soga and Yakuwa 1999). A long-term follow-up including pulmonary function tests, bronchoscopy, and chest CT, if necessary, is essential, since relapses can occur even after many years. Detected in a timely manner, relapses can be successfully treated with reoperation (Rizzardi et al. 2009).

Stage-dependent survival curves of bronchial carcinomas in adults are published by Goldstraw et al. 2007. 5-year overall survival (OS) (all tumor stages) is 15%. 5-year survival following surgery was: in stage I, 73–54%, in stage II, 48–38%, in stage III, 25–19%, and in stage IV, 21%, respectively (Goldstraw et al. 2007). For instance, in a prospective randomized phase III trial of the GLCCG for patients with stage III NSCLC, 5-year OS could be improved to 48%, if following neoadjuvant chemotherapy or additional chemoradiotherapy and complete resection (R0), mediastinal downstaging could be achieved (Thomas et al. 2008). Induction chemotherapy has also been used to improve complete resection rate and does not appear to increase operative mortality in experienced thoracic surgeons.

There are only little data on survival of children, adolescents, and young adults with lung cancer. In 2009, Neville et al. (2009) published data of the SEER

registry from 1973 to 2004 for all patients with pulmonary tumors less than 20 years of age. They demonstrated that the incidence of pediatric lung cancer remains stable. The most common histology was endocrine tumor, followed by sarcoma and mucoepidermoid tumor. The mean age at diagnosis was 16 years. In their multivariate analysis, surgical treatment and endocrine histology were independent prognostic factors for survival.

In the Detroit SEER registry (from 1973 to 1992), overall and stage-dependent 5-year relative survival rates were significantly better in the younger patient group (<50year) (16.1% vs. 13.4%) (Ramalingam et al. 1998). Of 31,266 patients, 9% were under 50 years of age at diagnosis, 1.2% under 40 years, and 0.07% under 30 years. Treatment was managed in a more aggressive fashion than in older patients due to their better overall medical condition. Younger patients had a higher incidence of adenocarcinoma as histologic subtype (Ramalingam et al. 1998; Kreuzer et al. 1999).

LUCY (Lung Cancer in the Young) is an ongoing multicenter trial with 30 participating clinics all over Germany. From 2000 up to now, more than 800 young patients (<50 years) with primary lung cancer have been recruited with phenotype data. Current studies are candidate gene association studies and functional analyses of genotyping (Sauter et al. 2008). Many epidemiologic and clinical studies have indicated familial aggregation of lung cancer. Kreutzer could demonstrate a threefold increase in risk of lung cancer in patients younger than 46 years if relatives were also affected by lung cancer (Kreuzer et al. 1998). Several studies conducted in the last decades reported a preponderance of adenocarcinoma in young patients (Kreuzer et al. 1999). Although smoking is considered to be the predominant risk factor, only 10% of heavy smokers develop lung cancer. This suggests that genetic variation in sensitivity to carcinogen exposure can play an important role in the etiology of lung cancer (Sauter et al. 2008) Timofeeva et al. 2009.

Due to low incidence of lung cancer in children, adolescents and young adults will be presented in case reports or registry data, only. In future protocols, individualized and targeted therapies will be applied directed to tumor molecular markers and other tumor prognostic markers as in adult patients. Since there is no obvious evidence that histologically identical tumors differ biologically by age, these study data from young adults can be transferred to the treatment of adolescents and even children. However, data collection should be ensured, ideally to pediatric rare tumor registries that include experts from internal and surgical oncology.

References

Asamura H, Kameya T, Matsuno Y et al (2006) Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 24(1):70–76

Bini A, Brandolini J, Cassanelli N et al (2008) Typical and atypical pulmonary carcinoids: our institutional experience. Interact Cardiovasc Thorac Surg 7(3):415–418

Cohen MC, Kaschula RO (1992) Primary pulmonary tumors in childhood: a review of 31 years' experience and the literature. Pediatr Pulmonol 14(4):222–232

Davila DG, Dunn WF, Tazelaar HD, Pairolero PC (1993) Bronchial carcinoid tumors. Mayo Clin Proc 68(8):795–803

de Christenson ML Rosado, Abbott GF, Kirejczyk WM, Galvin JR, Travis WD (1999) Thoracic carcinoids: radiologic-pathologic correlation. Radiographics 19(3):707–736

Detterbeck FC (2010) Review: management of carcinoid tumours. Ann Thorac Surg 89:998–1005

Filosso PL, Rena O, Donati G et al (2002) Bronchial carcinoid tumors: surgical management and long-term outcome. J Thorac Cardiovasc Surg 123(2):303–309

Goeckenjan G, Sitter H, Thomas M et al (2010) Prevention, diagnosis, therapy, and follow-up of lung cancer. Interdisciplinary guideline of the German Respiratory Society and the German Cancer Society. Pneumologie 64(suppl2):S23–S155

Goldstraw P, Crowley J, Chansky K et al (2007) The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2:706–720

Gustafsson BI, Kidd M, Modlin IM (2008) Neuroendocrine tumors of the diffuse neuroendocrine system. Curr Opin Oncol 20(1):1–12

Hartman GE, Shochat SJ (1983) Primary pulmonary neoplasms of childhood: a review. Ann Thorac Surg 36(1):108–119

Jager PL, Chirakal R, Marriott CJ, Brouwers AH, Koopmans KP, GulenchynKY(2008)6-L-18F-fluorodihydroxyphenylalanine PET in neuroendocrine tumors: basic aspects and emerging clinical applications. J Nucl Med 49(4):573–586

Janne PA, Wang XF, Socinski MA et al (2010) Randomized phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 (abstract #7503). J Clin Oncol 28:539s

Klöppel G (2007a) Oberndorfer and his successors: from carcinoid to neuroendocrine carcinoma. Endocr Pathol 18(3):141–144

Klöppel G (2007b) Tumour biology and histopathology of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 21(1):15–31

Koopmans KP, Neels OC, Kema IP et al (2008) Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. J Clin Oncol 26(9):1489–1495

Kreuzer M, Kreienbrock L, Gerken M et al (1998) Risk factors for lung cancer in young adults. Am J Epidemiol 147:1028–1037

Kreuzer M, Kreienbrock L, Müller K et al (1999) Histologic types of lung carcinoma and age at onset. Cancer 85:1958–1965

McCahon E (2006) Lung tumours in children. Paediatr Respir Rev 7(3):191–196

Neville H, Hogan A, Zhuge Y et al (2009) Incidence and outcomes of malignant pediatric lung neoplasms. J Surg Res 156:224–230

Oberndorfer S (1907) Karzinoide tumoren des dünndarms. Frankf Zschr Pathol 1:426–432

Ramalingam S, Pawlish K, Gadgeel S et al (1998) Lung cancer in young patients: analysis of a surveillance, epidemiology, and end results database. J Clin Oncol 16:651–657

Rizzardi G, Marulli G, Calabrese F et al (2009) Bronchial carcinoid tumours in children: surgical treatment and outcome in a single institution. Eur J Pediatr Surg 19(4): 228–231

Robinson LA, Ruckdeschel JC, Wagner H et al (2007) Treatment of stage IIIA non-small cell lung cancer. ACCP evidence-based clinical practice guidelines (2nd ed). Chest 132: 243–265

Rosenberger A, Illig T, Korb K et al (2008) Do genetic factors protect for early onset lung cancer? A case control study before the age of 50 years. BMC Cancer 8:60–71

Sachithanandan N, Harle RA, Burgess JR (2005) Bronchopulmonary carcinoid in multiple endocrine neoplasia type 1. Cancer 103(3):509–515

Sauter W, Rosenberger A, Beckmann L et al (2008) Matrix Metalloproteinase 1 (MMP1) is associated with early-onset lung cancer. Cancer Epidemiol Biomarkers Prev 17(5):1127–1135

Soga J, Yakuwa Y (1999) Bronchopulmonary carcinoids: an analysis of 1,875 reported cases with special reference to a comparison between typical carcinoids and atypical varieties. Ann Thorac Cardiovasc Surg 5(4):211–219

Srirajaskanthan R, Toumpanakis C, Karpathakis A et al (2009) Surgical management and palliative treatment in bronchial neuroendocrine tumours: a clinical study of 45 patients. Lung Cancer 65(1):68–73

Thomas M, Rübe C, Hoffknecht P et al (2008) Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomized trial in stage III non-small-cell lung cancer. Lancet Oncol 9:636–648

Timofeeva M, Kropp S, Sauter W et al (2009) CYP450 polymorphisms as risk factors for early-onst lung cancer: gender-specific differences. Carcinogenesis 30(7):1161–1169

Wang LT, Wilkins EW Jr, Bode HH (1993) Bronchial carcinoid tumors in pediatric patients. Chest 103(5):1426–1428

Ward PS, Mott MG, Smith J, Hartog M (1984) Cushing's syndrome and bronchial carcinoid tumour. Arch Dis Child 59(4):375–377

Winton T, Livingston R (2004) A prospective randomized trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage I B and II non-small cell lung cancer (NSCLC): intergroup JBR 10. J Clin Oncol 22: 621–626

Pediatric Pleural Mesothelioma

27

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27.1 Introduction

Malignant mesothelioma is an aggressive tumor that originates from the lining cells (mesothelium) that cover the serosal surfaces of the pleural and peritoneal cavities, or more rarely the tunica vaginalis testis and the pericardium (Moore et al. 2008). Based on the stage of the disease at the time of diagnosis, mesothelioma may present as discrete multifocal nodules or as a diffuse confluent mass encasing the adjacent organs and/or obliterating the serosal cavity from which the tumor has originated.

Although before the 1950s, the existence of adults mesothelioma was questioned by many pathologists (Moore et al. 2008), the increase in the incidence of mesothelioma, ensuing to the growing use of asbestos, definitely led to the acknowledgment of mesothelioma as a genuine clinicopathologic entity (Margery and Ruffié 2008). In children, because this is an even rarer tumor, its existence has long been debated and consequently its management neglected. Furthermore, because of the rarity of mesothelioma and the consequent difficulty in its diagnosis, a significant proportion of cases that have been diagnosed initially as pediatric mesothelioma were found to represent other entities upon a subsequent second pathological analysis (Fraire et al. 1988). Nevertheless, recent small series have been published using state-of-the-art adults diagnosis criteria (Moran et al. 2008). These recent studies have established the existence of pediatric mesothelioma and highlighted the lack of optimal strategy.

We will focus here on pleural mesothelioma and exclude peritoneal mesothelioma (see specific. Chap 43) as well as mesothelioma of the tunica vaginalis and

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Table 27.1 Key points to manage a child with pleural mesothelioma

Physical examination	Signs and symptoms (cough, dyspnea, fatigue, pallor, weight loss) Anamnesis: asbestosis exposure
Laboratory assessment	None specific
Radiological assessment	
- first assessment **- local staging**	Abdominal Computed Tomography (CT) scan
- diagnostic work-up	Chest and abdominal CT scan, Positron Emission Tomography (PET) MRI Cardiac echography
Pathological assessment	Surgical biopsy required Always need adult's pathologist experienced with mesothelioma To get confirmation of the diagnosis of malignant mesothelioma and subtype Application of an appropriate panel of immunochemical stains
Staging systems for risk-adapted treatment strategy	None validated
General treatment guidelines	Need for multidisciplinary approach Seek for national or European group for rare tumors advice Seek advice from centre with expert physician dedicated to the management of this cancer in adults
Surgery	Consider complete resection when it can be easily removable
Radiotherapy	Can be considered as part of multimodal therapy
Chemotherapy	First line : premetrexed-cisplatinum Second line or alternative : gemcitabine-pemetrexed Consider treatment with novel agents validated in adults

pericardial mesothelioma. The main challenge for pediatric oncologists remains to choose the optimal therapeutic strategy for a given patient. These options range from upfront palliative care to aggressive multimodal treatments. Meanwhile, we must increase our knowledge about this disease to codify its management (Table 27.1).

27.2 Epidemiology

In adults, it is estimated that mesothelioma represents less than 0.5% of all cancers. Among malignant mesothelioma, pleural mesothelioma is the most common localization (Fig. 27.1). In children, pleural mesothelioma is an extremely rare disease and no precise incidence of this disease is available. Our knowledge relies mostly on isolated case reports and rare small series. Of note, the first pediatric series was published in 1964 by Kauffman and Stout who reported five cases of both peritoneal and pleural mesothelioma (Kauffman and Stout 1964). Based on results of autopsies, pediatric mesothelioma would represent 2–5% of all mesothelioma cases, and according to epidemiologic studies would represent 0.5–1.0 case/10 millions/year (Kashanskiy and André 2010). We previously reviewed and reported epidemiologic data of 489 cases of pediatric mesothelioma; pleural mesothelioma represented approximately 60% of the cases, in line with other less extensive reviews of the literature (Fraire et al. 1988; Anderson et al. 1985).

As in adults, there is a higher frequency of pleural mesothelioma in boys (Kauffman and Stout 1964; Kashanskiy and André 2010; Brenner et al. 1981), with a sex ratio of 1.3: 1 (Kashanskiy and André 2010). The mean age at presentation was 13.0 ± 0.3 years, with no difference between sexes (Kashanskiy and André 2010).

There is a strong relationship between exposure to asbestos and the subsequent development of pleural mesothelioma in adults (Moore et al. 2008). Nevertheless, in our experience, there was no such association in children. Indeed, we found only five cases with a known previous exposure to asbestos among the 110 pediatric pleural mesothelioma cases for which the exposure to asbestos was well documented (Kashanskiy and André 2010). In line with this observation, the reported pediatric cases with a prior exposure to asbestos are anecdotal. Moreover, in many countries in which the exposure to asbestos is high because of the presence of mines like in

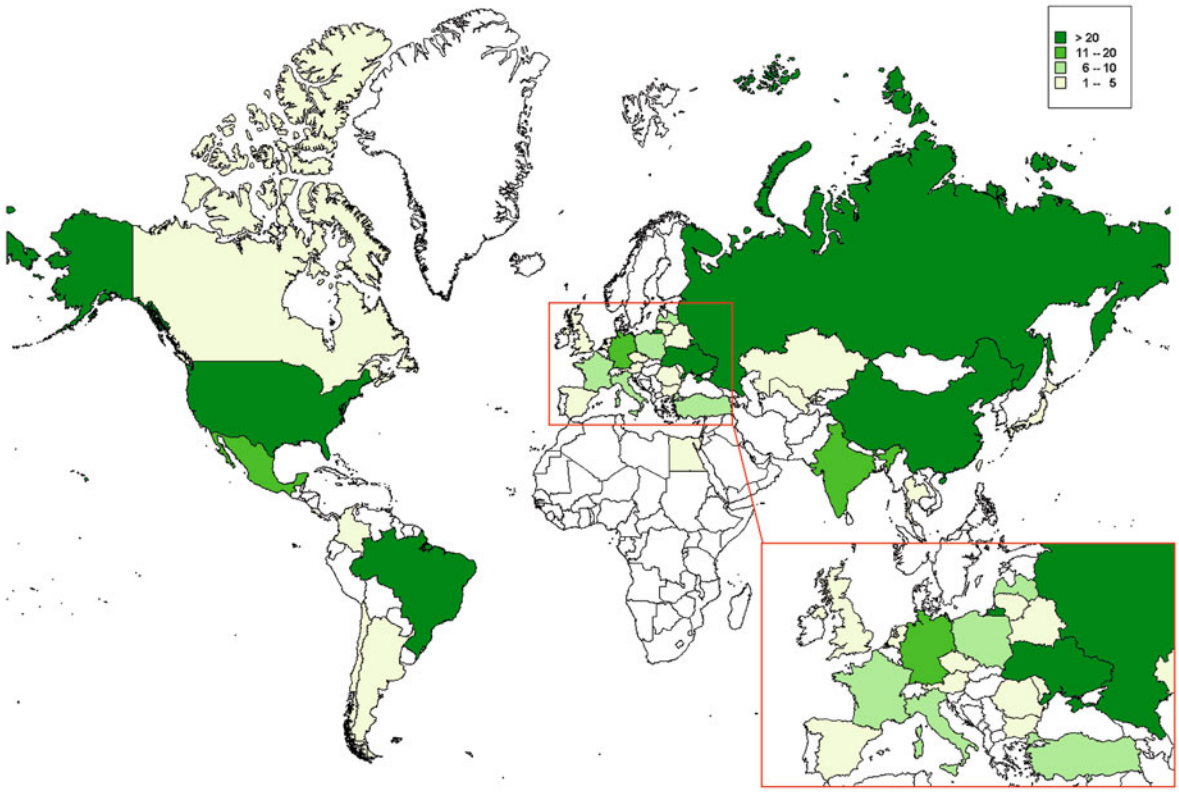

Fig. 27.1 Geographical distribution of published cases of pediatric pleural mesothelioma

Australia, Finland, or the South African Republic, no cases have been reported. Lastly, it is generally accepted that it takes approximately 20–30 years after asbestos exposure to develop a mesothelioma so that it seems very unlikely that asbestosis is implicated in the genesis of mesothelioma in children. Thus, most pediatric mesotheliomas might belong to the so-called idiopathic forms of mesothelioma, which can also occur in adults with an estimated incidence of 1/million (Moore et al. 2008).

Besides asbestos exposure, other predisposing factors have been implicated in the pathogenesis of mesothelioma in children; for instance, irradiation or genetic syndromes. These suggestions rely on reported cases of pleural mesothelioma occurring after irradiation (Anderson et al. 1985; André et al. 2009; Falchero et al. 1996), as secondary malignancies especially after a Wilms' tumor or Hodgkin's disease (Anderson et al. 1985; André et al. 2009; Falchero et al. 1996; Antman et al. 1984), or in children with Proteus syndrome (Gordon et al. 1995; Malamitsi-Puchner et al. 1990). These cases suggest that in some patients, a non-identified underlying genetic background may contribute to the occurrence of a mesothelioma. Mutation of WT1 has been reported in sporadic cases of mesothelioma (Park et al. 1993) and is also frequent in patients with Wilms' tumor (Haber and Buckler 1992). However, the role of this gene in the genesis and progression of the tumor is not clear (Park et al. 1993). Some familial cases of mesothelioma have been reported with a deletion of the short arm of chromosome 9 that carries the CDKN2A gene. This gene encodes for $p16^{INK4a}$ and $p14^{ARF}$. The inactivation of $p16^{INK4a}$ has been frequently reported in mesothelioma (You et al. 2007; Ugolini et al. 2008). Nevertheless, no children have been reported to be affected in these familial series.

27.3 Clinical Presentation

Typical presenting features of children with pleural mesothelioma are chest pain, dyspnoea, or both in most of the cases (Fraire et al. 1988; Kauffman and Stout 1964; Brenner et al. 1981; André et al. 2009).

These symptoms develop usually quickly in a previously nonsymptomatic child. Fever is sometimes an associated symptom. Additionally, patients may very rarely present with breathlessness secondary to a pleural effusion without chest pain. A chest wall mass, weight loss, and abdominal pain and ascites due to peritoneal involvement are also common presentations. Indeed in the SFCE series, involvement of multiple serosal cavities was seen in one third of the patients (André et al. 2009)

27.4 Radiological Presentation

Radiological imaging is critical for both the diagnosis and staging and in turn the management of mesothelioma.

27.4.1 CT

Intravenous contrast-enhanced CT is the primary imaging modality for suspected pleural malignant disease, where it can help distinguishing malignant from benign pleural disease. The most helpful CT findings suggesting a malignant pleural disease in adults are: (1) a circumferential pleural rind, (2) nodular pleural thickening, (3) diffuse pleural thickening, and (4) mediastinal pleural involvement. While these features have a high positive predictive value, absence of these signs does not reliably exclude the diagnosis of pleural malignancy (Moore et al. 2008; Wang et al. 2004)

27.4.2 MRI

In adults, MRI is not used routinely to assess malignant mesothelioma. However, it can be a valuable tool to confirm the potential surgical resectability. More specifically, using gadolinium enhancement, MRI can improve the identification of tumor extension into the diaphragm or chest wall, allowing better assessment of the individual for surgical treatment (Moore et al. 2008; Wang et al. 2004).

27.4.3 PET Scan

PET scan has been reported to have a 97% sensitivity and a 88% specificity to distinguish benign from malignant pleural disease in adults (Moore et al. 2008). Additionally, PET scanning has also increased the accuracy to diagnose mediastinal nodal metastases so that overall PET scan is useful in the staging and preoperative evaluation of mesothelioma (Moore et al. 2008; Wang et al. 2004). PET scan may also help to identify the optimal site for CT-guided pleural biopsy. Lastly, changes in the fluorodeoxyglucose (FDG) uptake within the tumor might indicate response to treatment, suggesting its role to assess the response to chemotherapy. Nevertheless, the value of PET scan to adequately stage the disease remains controversial and its use in routine is not yet recommended in adults (Pilling and Dartnell 2010; Scherpereel et al. 2010). In children, very little is known regarding the use of PET scanning, but in one case, decrease in size and uptake of FDG by a mesothelioma was documented during a treatment with pemetrexed and cisplatinum (Milano et al. 2006).

27.5 Pathology

The pathological diagnosis of mesothelioma is acknowledged as difficult. As for adults, pathologic analysis should be performed on representative biopsy specimen obtained by surgery. Given the histological heterogeneity of mesothelioma and the fact that it may mimic a variety of epithelial and mesenchymal neoplasms, needle biopsies are commonly of limited value as diagnostic tool. It is generally recommended that all cases be confirmed by a panel of pathologists including one with experience in adults mesothelioma. According to the WHO classification, malignant mesothelioma can be classified into epithelioid, sarcomatoid, or mixed (biphasic) subtypes based on tissue obtained by biopsy. The majority (almost 60%) of pediatric pleural mesotheliomas are of the epithelial subtype (Kashanskiy and André 2010).

On scanning magnification, the tumor classically displays sheets of medium-sized or large epithelioid cells with distinct cell borders arranged into well-developed tubulo-papillary structures, commonly with intermixed solid areas and occasional adenomatoid pattern. At higher magnification, tumor cells have a bland cytological appearance, being polygonal in shape, with moderate amount of pale eosinophilic cytoplasm, round nuclei, and inconspicuous nucleoli (Fig. 27.2). Usually, only rare mitotic figures can be

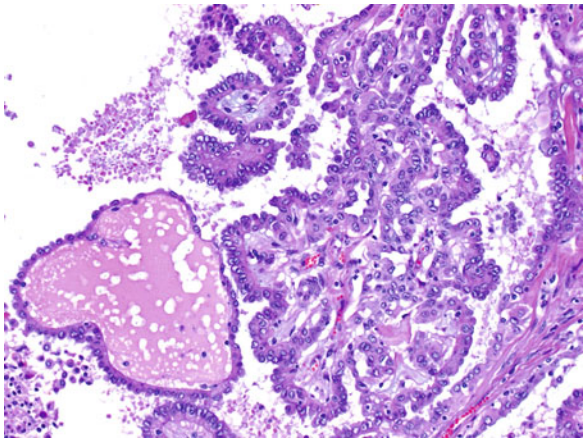

Fig. 27.2 Typical tubulopapillary pattern of mesothelioma with relatively bland-looking cuboidal cells (H&E stain, original magnification ×200)

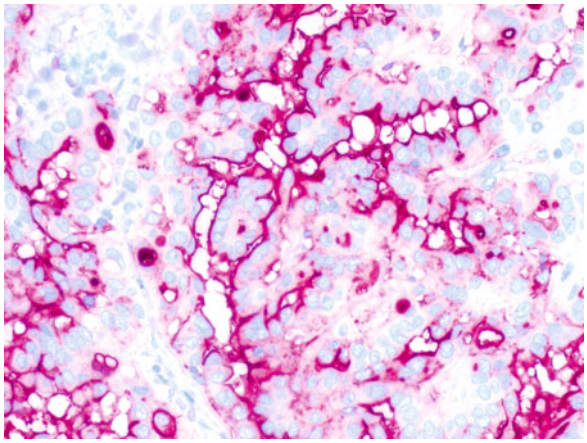

Fig. 27.3 HBME-1 showed characteristic apical (luminal) membranous staining in msothelioma cells

identified (<1/mm^2). In some areas, the epithelioid cells form gland-like structures and communicating cords set within abundant mucinous or myxoid stroma (Moran et al. 2008; Brenner et al. 1981; Anderson et al. 1985). The tubules occasionally contain a wispy bluish secretion that stains positive with alcian blue and disappears after predigestion with hyaluronidase. In contrast to adenocarcinoma, true PAS-positive mucin is usually absent in mesothelioma.

Traditionally, a panel of positive and negative immunohistochemical markers is recommended to reliably diagnose mesothelioma. The tumor cells commonly express mesothelin, HBME-1 (Fig. 27.3) cytokeratin (CK) 5/6, calretinin, D2–40 (podoplanin), and vimentin. The low-molecular-weight CK (CAM5.2) is helpful in identifying less well-differentiated tumors that have lost other differentiation markers. More recently, Wilms' tumor-1 antigen (WT1) proved of value as a further marker. However, given the fair expression of this marker by serous carcinomas of the female genital tract, careful interpretation in the appropriate context is necessary. Markers that are usually absent in mesothelioma but are variable expression in carcinomas include Ber-EP4, carcinoembryonic antigen (CEA), and thyroid transcription factor 1 (TTF-1).

27.6 Treatment

In adults, no standard optimal treatment strategy is currently available owing to the rarity of this tumor and the limited efficacy of treatments. Recent data and guidelines in adults suggest that multimodal (extrapleural pneumectomy–neoadjuvant/adjuvant chemotherapy and radical hemithorax irradiation) should be proposed to patients when possible (Scherpereel et al. 2010) and within prospective randomized trials. Nothing is known about this global strategy in children; the aggressive surgery and its related mortality and morbidity, as well as radiotherapy associated side effects should make one highly cautious about using this strategy in children.

27.6.1 Surgery

Surgery aiming at removal of all malignant tissue is only very rarely associated with persistent durable complete remission as the disease usually has spread, at least microscopically, within the pleural cavity. Some examples can be found in pediatric literature (Flores et al. 2006). Therefore, we advocate for complete surgery only in cases of easily removable tumor. Besides, pleurectomy/decortication can be proposed but without curative intent and considered in patients to help obtaining symptom control.

27.6.2 Chemotherapy

While the combination of pemetrexed–cisplatinum is a standard first-line chemotherapy in adults with pleural mesothelioma (Vogelzang et al. 2003), there is currently no such standard chemotherapy regimen for pleural

mesothelioma in children. Anyhow, these new molecules (pemetrexed, gemcitabine) indeed seem to bring clinical benefit for children with mesothelioma (Antman et al. 1984; Ugolini et al. 2008; Milano et al. 2006). Recent studies have shown molecular alterations (mutations) involving the EGFR signalling pathway in about one third of adults mesothelioma. These findings might bring a new hope by targeting these molecular pathways in analogy to the current treatment regimens for EGFR-mutated non-small-cell lung cancer, but this remains an issue of future studies.

27.6.3 Radiotherapy

Radiotherapy has not been demonstrated to be an effective treatment in mesothelioma in adults (Scherpereel et al. 2010), and its use is mostly restricted to try to control disease for patients receiving palliative care. As mentioned above, in adults radical hemithorax radiotherapy has been proposed within a multimodal strategy (Scherpereel et al. 2010).

27.6.4 Outcome

Historically, the prognosis of pleural mesothelioma in children had been reported to be extremely poor. Thus, Grundy and Miller reported that death occurred within 6 months in 8 out of 12 patients with pleural mesothelioma, with the longest survival being 24 months (Grundy and Miller 1972). A more recent review only partially confirmed these findings. Indeed, the authors also reported long-term survival in two children (66 and 84 months), among whom one was treated with standard MTD chemotherapy (Brenner et al. 1981). Interestingly, Mutafoglu-Uysal et al. reported a case of relapsing malignant pleural mesothelioma that responded to the combination of VAC–ICE chemotherapy and who was alive without evidence of disease 36 months after discontinuation of the treatment (Mutafoğlu-Uysal K et al. 2002). Additional cases responding to MTD chemotherapy have been reported (Kung et al. 1995). Thus, although, we should be ready to face rapid progression and refractory disease, in some cases pediatric pleural mesothelioma can respond to chemotherapy and be long-term survivors. Biologic and/or genetic differences underlying this difference of behavior must be unveiled.

27.7 Conclusion

Mesothelioma is a very rare tumor in pediatric oncology. Pediatric mesothelioma seems to be different from its adults counterpart, with less frequent primary pleural localization. Although the outcome of children with peritoneal mesothelioma is good despite frequent relapses, the outcome of pediatric pleural mesothelioma is dismal. This is in line with data obtained from adults. New therapeutic strategies need to be properly evaluated in children within international studies, and an international registry is mandatory to increase our knowledge of this disease.

References

Anderson KA, Hurley WC, Hurley BT et al (1985) Malignant pleural mesothelioma following radiotherapy in a 16-year-old boy. Cancer 56:273–276

André N, Ratsimandresey R, Réguerre Y et al (2009) Paediatric malignant mesothelioma: the SFCE experience. Pediatr Blood Cancer 53:823

Antman KH, Ruxer RL Jr, Aisner J et al (1984) Mesothelioma following Wilms' tumor in childhood. Cancer 54:367–369

Brenner J, Sordillo PP, Magill GB (1981) Malignant mesothelioma in children: report of seven cases and review of the literature. Med Pediatr Oncol 9:367–373

Falchero L, Coiffier B, Guibert B et al (1996) Malignant mesothelioma of the pleura following radiotherapy for Hodgkin disease. Bull Cancer 83:964–968

Flores RM, Su W, Lal D, Rusch VW, La Quaglia MP (2006) Extrapleural pneumonectomy in children. J Pediatr Surg 41:1738–1742

Fraire AE, Cooper S, Greenberg SD et al (1988) Mesothelioma of childhood. Cancer 62:838–847

Gordon PL, Wilroy RS, Lasater OE et al (1995) Neoplasms in Proteus syndrome. Am J Med Genet 57:74–78

Grundy GW, Miller RW (1972) Malignant mesothelioma in childhood. Cancer 5:1216–1218

Haber DA, Buckler AJ (1992) WT1: a novel tumor suppressor gene inactivated in Wilms' tumor. New Biol 4:97–106

Kashanskiy SV, André N (2010) Paediatric mésothelioma: is there the such a disease? Bull Cancer 97:571–576

Kauffman SL, Stout AP (1964) Mesothelioma in children. Cancer 17:539–544

Kung FH, Desai SJ, Dickerman JD et al (1995) Ifosfamide/carboplatin/etoposide (ICE) for recurrent malignant solid tumors of childhood: a pediatric oncology group phase I/II study. J Pediatr Hematol Oncol 17:265–269

Malamitsi-Puchner A, Dimitriadis D, Bartsocas C et al (1990) Proteus syndrome: course of a severe case. Am J Med Genet 35:283–285

Margery J, Ruffié P (2008) Environmental cancer: malignant pleural mesothelioma. Bull Cancer 95:77–86

Milano E, Pourroy B, Rome A, Delarue A et al (2006) Efficacy of a combination of pemetrexed and multiple redo-surgery in

an 11-year-old girl with a recurrent multifocal abdominal mesothelioma. Anticancer Drugs 17:1231–1234

Moore AJ, Parker RJ, Wiggins J (2008) Malignant mesothelioma. Orphanet J Rare Dis 3:34

Moran CA, Albores-Saavedral J, Suster S (2008) Primary peritoneal mesotheliomas in children: a clinicopathological and immunohistochemical study of eight cases. Histopathology 52:824–830

Mutafoğlu-Uysal K, Kargi A, Sarialioğlu F, et al. (2002) Malignant pleural mesothelioma in a child: long-term survival with ICE-WAC chemotherapy regimen. Turk J Pediatr. 44(3):244–247

Park S, Schalling M, Bernard A et al (1993) The Wilms tumour gene WT1 is expressed in murine mesoderm-derived tissues and mutated in a human mesothelioma. Nat Genet 4: 415–420

Pilling J, Dartnell JA (2010) Lang-lazdunski L integrated positron emission tomography-computed tomography does not accurately stage intrathoracic disease of patients undergoing trimodality therapy for malignant pleural mesothelioma. Thorac Cardiovasc Surg 58:215–219

Scherpereel A, Astoul P, Baas P et al (2010) Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J 35:479–495

Ugolini D, Neri M, Ceppi M et al (2008) Genetic susceptibility to malignant mesothelioma and exposure to asbestos: the influence of the familial factor. Mutat Res 658: 162–167

Vogelzang NJ, Rusthoven JJ, Symanowski J et al (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636–2644

Wang ZJ, Reddy GP, Gotway MB, Higgins CB, Jablons DM, Ramaswamy M, Hawkins RA, Webb WR (2004) Malignant pleural mesothelioma: evaluation with CT, MR imaging, and PET. Radiographics 24:105–119

You B, Blandin S, Gérinière L et al (2007) Mésothéliomes familiaux: une composante génétique associée aux risques environnementaux? Bull Cancer 7:705–710

Thymoma and Thymic Carcinoma

28

Jan Godzinski

Contents

Thymoma and thymic carcinoma are infrequent epithelial tumors occurring usually in older adults in fourth to sixth life decade, constituting only 0.2–1.5% of all malignancies (Voitz et al. 1997). The classification system, risk factors and treatments have been developed in adults and have been transferred to the treatment of children and adolescents. Pediatric experience, however limited, confirms that characteristics of this disease probably do not change with age. In children, thymomas and thymic carcinomas contribute less than 1% to all mediastinal tumors (Ramon and Suster 1991). Larger multi-center pediatric studies are necessary to definitely confirm this statement (Stachowicz-Stencel et al. 2010; Yaris et al. 2006). Despite low incidence in childhood, it is important to keep in mind this rare condition. On one hand, 30–50% of cases are asymptomatic and recognized incidentally at X-ray performed for other reasons, such as respiratory infection. On the other hand, 30–65% of patients suffer from autoimmune paraneoplastic syndromes related to thymoma. Among these, myasthenia gravis is observed most commonly (Schmidt-Wolf et al. 2003).

28.1 Definition

Thymoma and thymic carcinoma are epithelial tumors of thymus.

28.2 Pathologic Classification and Staging

The currently used WHO histopathological classification system categorizes the tumors according to the phenotype of the epithelial component and the amount of infiltrating

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Table 28.1 Staging system of epithelial thymic tumors according to Masaoka (1981)

Stage	Definition
1	Completely resected encapsulated tumor
2A	Capsular invasion and/or microscopic invasion of mediastinal fatty tissue or pleura
2B	Macroscopic invasion of mediastinal fatty tissue or pleura
3	Invasion per continuitatem into organs (pericardium, lungs, great vessels)
4A	Macroscopic pleural or pericardial implants
4B	Distant lymphogenous and/or hematogeneous metastases

T-lymphocytes (see Chap. 23). Thymomas are categorized into type A and B thymomas. The majority of childhood thymomas fall into the "B" category. The WHO system closely corresponds to predictable outcomes. Type A (medullary thymoma) and AB (mixed thymoma) are prognostically favorable and show a 100% event-free survival at 10 years. The event-free survival rates for B1 (lymphocytic thymoma) and B2 (cortical thymoma) are 83%; for B3 (atypical thymoma), 38%; and type C (thymic carcinoma), 28%, respectively (Chen et al. 2002). The most important histopathological differential diagnoses are extensively discussed in Chap. 23.

The most commonly used clinical staging system is that of Masaoka (Table 28.1) (Masaoka et al. 1981). It describes the most important clinical/surgical observations. In brief, stage 1 corresponds to encapsulated tumors; stage 2, tumors with microscopical (2a) and macroscopical (2b) invasion of the surrounding fatty tissue and mediastinal pleura; stage 3, macroscopical invasion into the neighboring organs; and stage 4, dissemination of the disease to pleura or pericardium (4a) or lymphogenous or hematogenous metastasis (4b). Some authors postulate that the value of clinical staging is more important in case of less aggressive variants of pathology. However, the rationale of this assumption is not quite clear. The pathology variant is the primary factor which influences the dynamics of the disease, and not vice versa (Masaoka et al. 1991; Stachowicz-Stencel et al. 2003).

28.3 Molecular Implications

In a genetic survey with comparative genomic hybridization, B3 thymomas commonly show gain of 1q, loss of chromosome 6 and loss of 13q. The number of genomic imbalances is higher in thymic squamous cell carcinomas. Recurrent imbalances include losses of 16q, 6, 3p and 17p and gains of 1q, 17q and 18. This study suggests that B3 thymomas and primary thymic squamous cell carcinoma have similar molecular aberrations (Zetti et al. 2000).

28.4 Paraneoplastic Autoimmune Syndromes

The spectrum of autoimmune disorders includes myasthenia gravis, peri- and myocarditis, polymyositis, lupus erythematosus, rheumatoid arthritis, thyroiditis, Sjögren syndrome, aplastic and hemolytic anemia, Addison disease, Cushing syndrome, scleroderma, limbic encephalopathy, nephrotic syndrome, radiculopathy and others (Levy et al. 1998; Schmidt-Wolf et al. 2003; Stachowicz-Stencel et al. 2003; Thomas et al. 1999). The pathway of the autoimmune syndromes relates to the alteration of the circulating T-cells (Buckley et al. 2001; Hoffacker et al. 2000), B-cell lymphopenia (Levy et al. 1998; Ritter and Wick 1999) and to the antibodies to several neuromuscular antigens, namely, acetylcholine and striated muscle receptors (Gautel et al. 1993; Voitz et al. 1997; Emir et al. 2001).

28.5 Diagnosis

Despite the high relative frequency of the paraneoplastic syndrome in association with thymoma and thymic carcinoma, a significant proportion of patients (30–50%) are diagnosed incidentally following chest X-ray performed for unrelated reasons. The tumor-related symptoms related to the disease may include cough, dyspnea, chest pain, respiratory distress and superior vena cava syndrome (Emir et al. 2001; Hoffacker et al. 2000; Schmidt-Wolf et al. 2003; Stachowicz-Stencel et al. 2003; Yaris et al. 2006).

The conventional chest X-ray is not precise enough since thymomas and thymic carcinomas locate in the anterior mediastinum and develop predominantly in one lobe of the thymus. Good quality CT or MRI offer much more precise information that is clinically and surgically useful and allows for better differentiation from other anterior mediastinum pathologies. Those include Hodgkin and non-Hodgkin lymphomas, germ-cell tumors including teratomas, thymic cysts

and, in rare cases, neuroblastomas. For clinical distinction of neuroblastomas, which predominantly develop in the posterior mediastinum, the measurement of catecholamine metabolites may be used. The assessment of alpha-1 fetoprotein, human chorionic gonadotropin and human placenta-like alkaline phosphatase may help in excluding malignant germ-cell tumors that may develop within the thymus (Schneider et al. 2000). Also, non-neoplastic thymic hypertrophy (e.g. rebound thymic hypertrophy which may follow completing of the cytotoxic chemotherapy) may mimic a thymic tumor.

28.6 Treatment

Initial biopsy allows for precise microscopic diagnosis, and it is never a mistake. The biopsy may be performed frequently in minimal invasive way. The techniques of mediastinoscopy, thoracoscopy or small supra- or perimanubrial open accesses are well developed and safe. However, it should be noted that in small needle core biopsy, definite histopathological categorization may be impossible (see Chap. 23). In case of small stage 1 lesions, primary resection is also acceptable; however, any primary aggressive surgery is justified. It is important to always keep in mind that another probable and more frequent differential diagnosis is malignant Hodgkin or T-cell lymphoma, which are both curable with chemotherapy and do not require surgical resection. However, these are usually not associated with autoimmune disorders, which may assist in therapeutic decision-making.

Once the diagnosis is clear, the treatment shall be planned. Surgery is the mainstay of therapy. In unresectable tumors that are histologically categorized as type C lesion, cisplatin-based chemotherapy is effective to some extent. However, optimal regimen has not yet been defined. Chemotherapy may also be used in a neo-adjuvant treatment setting, turning the tumor resectable. Neo-adjuvant strategies appear to gain more and more importance (Kim et al. 2004). Irradiation may be applied in desperate cases when surgeon cannot offer completeness of the tumor excision. However, the dose of 60 Gy, which is recommended in adults, is hardly acceptable in children (Nonaka et al. 2004) and may be associated with severe sequelae, such as radiogenic spinal damage (Stachowicz-Stencel et al. 2003).

Current reports have started focusing on targeted therapy with kinase inhibitors for thymic carcinomas with c-*kit* mutations (Ströbel et al. 2004, 2010). Thus, kinase inhibitors such as sunitinib may provide promising therapeutic potential in malignant thymic tumors that are either metastatic or not assessable to complete surgical therapy.

28.7 Summary and Comments

The optimal treatment for children's thymoma and thymic carcinoma, especially in stages higher than 1, is still unknown. Due to the unfavorable results in B3 and C tumors, surgeons shall be encouraged to attempt the most complete resection safely possible. The surgical risk can be reduced if cardiac surgeon and cardiopulmonary bypass devices are available.

Personal experience of the author indicates that if such conditions are available, resections can be bravely more aggressive and complete in a significant proportion of tumors at stages over 1. The surgery-related complications, if they occur, are manageable by an experienced multidisciplinary team without taking an unacceptable risk of morbidity and mortality. In the future, targeted therapy may provide new perspectives for successful treatment of unresectable tumors. International cooperation among pediatric surgeons and oncologists may thus help in evaluating such treatment modalities in these rare tumors.

References

Buckley C, Doudek D, Newsom-Davis J et al (2001) Mature, long-lived CD4 + and CD8 + T cells are generated by the thymoma in myasthenia gravis. Ann Neurol 50(1):64–72

Chen G, Marx A, Wen-Hu C et al (2002) New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer 95:420–442

Emir S, Kutluk T, Topalğlu R et al (2001) Scleroderma in a child after chemotherapy for cancer. Clin Exp Rheumatol 19:221–223

Gautel M, Lakey A, Barlow DP et al (1993) Titin antibodies in myasthenia gravis: identification of a major immunogenic region of titin. Neurology 43(8):1581–1585

Hoffacker V, Schultz A, Tiesinga JJ et al (2000) Thymomas alter the T-cell subset composition in the blood: a potential mechanism for thymoma-associated autoimmune disease. Blood 96(12):3872–3879

Kim ES, Putnam JB, Komaki R, Walsh GL, Ro JY, Shin HJ, Truong M, Moon H, Swisher SG, Fossella FV, Khuri FR, Hong WK, Shin DM (2004) Phase II study of a multidisciplinary

approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 44:369–379

Levy Y, Afek A, Sherer Y et al (1998) Malignant thymoma associated with autoimmune diseases: a retrospective study and review of the literature. Semin Arthritis Rheum 28(2):73–79

Masaoka A, Monden Y, Nakahara K (1981) Follow-up study of thymomas with special reference to their clinical stages. Cancer 48:2485–2492

Nonaka T, Tamami Y, Higuchi H et al (2004) The role of radiotherapy for thymic carcinoma. Jpn J Clin Oncol 34:722–726

Ramony Cajal S, Suster S (1991) Primary thymic epithelial neoplasms in children. Am J Surg Pathol 15:466–474

Ritter JH, Wick MR (1999) Primary carcinomas of the thymus gland. Semin Diagn Pathol 16(1):18–31

Schmidt-Wolf IG, Rockstroh JK, Schüller H et al (2003) Malignant thymoma: current status of classification and multimodality treatment. Ann Hematol 82(2):69–76

Schneider DT, Calaminus G, Reinhard H, Gutjahr P, Kremens B, Harms D, Göbel U (2000) Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. J Clin Oncol 18:832–839

Stachowicz-Stencel T, Bien E, Balcerska A, Godzinski J et al (2010) Thymic carcinoma in children: a report from the polish pediatric rare tumors study. Pediatr Blood Cancer 54:916–920

Ströbel P, Hartmann M, Jakob A, Mikesch K, Brink I, Dirnhofer S, Marx A (2004) Thymic carcinoma with overexpression of mutated KIT and the response to imatinib. N Engl J Med 350:2625–2626

Ströbel P, Bargou R, Wolff A, Spitzer D, Manegold C, Dimitrakopoulou-Strauss A, Strauss L, Sauer C, Mayer F, Hohenberger P, Marx A (2010) Sunitinib in metastatic thymic carcinomas: laboratory findings and initial clinical experience. Br J Cancer 103:196–200

Thomas CR, Wright CD, Loehrer PJ (1999) Thymoma: state of the art. J Clin Oncol 17(7):2280–2289

Voitz RD, Albrich WC, Nägele A et al (1997) Paraneoplastic myasthenia gravis: detection of anti-MGT30 (titin) antibodies predicts thymic epithelial tumor. Neurology 49(5): 1454–1457

Yaris N, Nas Y, Cobanoglu U et al (2006) Thymic carcinoma in children. Pediatr Blood Cancer 47:224–227

Zetti A, Ströbel P, Wagner K et al (2000) Recurrent genetic aberrations in thymoma and thymic carcinoma. Am J Pathol 157(1):257–266

Part VII

Rare Tumors of the Gastrointestinal Tract

Pathology and Differential Diagnosis

29

Bahig M. Shehata and Sarah C. Shulman

Contents

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29.1 Gastrointestinal Stromal Tumor

29.1.1 Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor of the gastrointestinal tract (Figs. 29.1–29.5). They primarily affect middle-aged or older adults, and they occur only rarely in children and adolescents. It has been proposed that GIST arises from the interstitial cells of Cajal (Liegl-Atzwanger et al. 2010; Benesch et al. 2009; Kaemmer et al. 2009; Machairas et al. 2010; Shimomura et al. 2010). Besides GIST, the family of mesenchymal tumors includes plexosarcomas, leiomyoblastomas, leiomyosarcomas (LMS), gastrointestinal autonomic nerve tumors (GANT), and gastrointestinal pacemaker cell tumors (GIPACT). While extensive research has been done on adult GIST by the National Comprehensive Cancer Network, the European Society of Medical Oncology, and others, standard practice and guidelines for children affected by GIST have not yet been established (Benesch et al. 2009).

29.1.2 Presentation

Pediatric GIST is most commonly found in the stomach (typically in the antrum), although cases have been identified in the small intestine, colon/rectum, omentum, and abdominal wall (Benesch et al. 2009; Shimomura et al. 2010). The average size of the tumor is 5.7 cm in greatest dimension with a range of 1.5–35 cm. Some patients, even unaffected by an associated tumor syndrome, present with multiple tumors or tumors with numerous satellite lesions. Metastasis is not uncommon, and it typically presents in the liver

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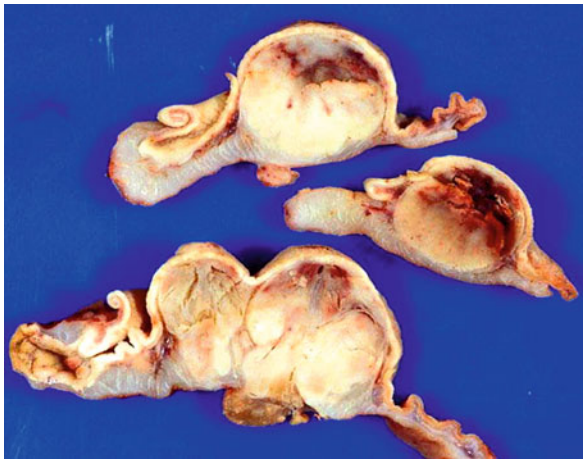

Fig. 29.1 Gastrointestinal stroma tumor: Multiple submucosal nodules showing gray–tan myxoid cut surface

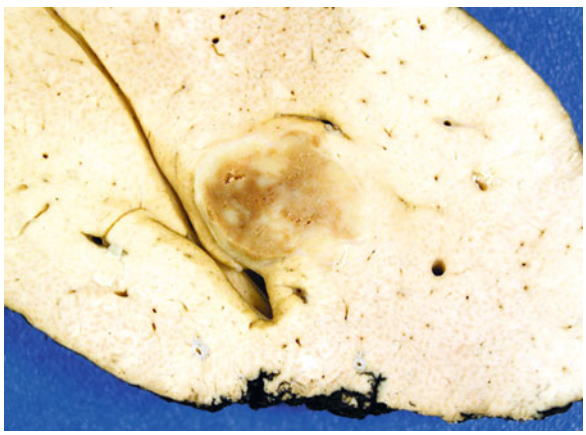

Fig. 29.2 Gastrointestinal stroma tumor: Liver metastasis from partial hepatectomy

(Fig. 29.2), lymph nodes, peritoneum, and mesentery. These lesions, however, rarely present at diagnosis (Benesch et al. 2009).

29.2 Pathology/Molecular Biological Findings

Pediatric gastric GISTs are most commonly epithelioid cell tumors (Fig. 29.3) or mixed spindle and epithelioid cell tumors; whereas in adults, spindle cell tumors are the most frequent (Shimomura et al. 2010). Two genes have been implicated in the pathogenesis of GIST: *KIT* and *PDGFRA* (4q11-q12). Both genes encode for transmembrane growth factor receptors which exhibit tyrosine kinase activity. The expression of these genes

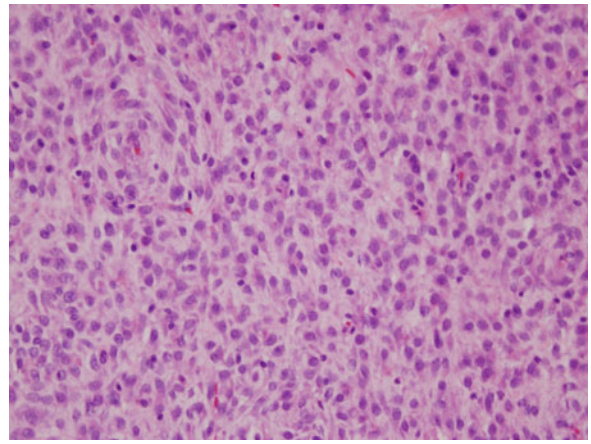

Fig. 29.3 Gastrointestinal stroma tumor: Sheets of epithelioid cells with neuroendocrine differentiation (400×)

leads to the activation of several pathways which regulate cell proliferation, adhesion, motility, and differentiation. These pathways include MEK-MAPK, STAT5, RAS, JAK2, and PI3-AKT (Liegl-Atzwanger et al. 2010; Machairas et al. 2010). Both mutations are early events in the development GIST. Researchers have found that these mutations are not involved in the malignant transformation of this tumor, only in the development and proliferation. In approximately 66% of mutated GISTs, monosomy 14 or partial loss of 14q is identified, and in approximately 50%, loss of 22q is identified. The latter is associated with the progression of GIST to a borderline or malignant lesion. Losses on chromosomes 1p, 9q, 11p, and 17q and gains on chromosomes 8q and 17q have also been identified, albeit their occurrence is rare. These mutations are also linked with malignancy. Both adult and pediatric GISTs without *KIT* or *PDGFRA* mutations display a much lower level of cytogenetic progression than mutant GISTs (Liegl-Atzwanger et al. 2010).

Expression of *KIT* is integral for the growth and preservation of cell types including germ cells, hematopoietic cells, mast cells, melanocytes, interstitial cells of Cajal, and intestinal pacemaker cells. Along with GIST, mutations in *KIT* have been identified in mast cell tumors, myelofibrosis, chronic myelogenous leukemia, and germ cell tumors. Mutations in the c-kit proto-oncogene have also been associated with the activation of the *KIT* receptor, leading to constant proliferation (Machairas et al. 2010). Mutations in *KIT* exist on exon 11 (68%), exon 9 (11%), exons 13 and 17 (0.6–4%) (Liegl-Atzwanger et al. 2010; Kaemmer et al. 2009; Machairas et al. 2010).

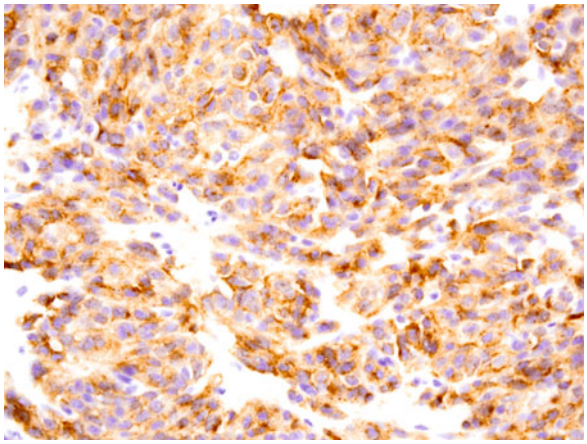

Fig. 29.4 Gastrointestinal stroma tumor: Strong positive c-kit immunohistochemical stain

When a *KIT* mutation is not indentified in GIST, typically a *PDGFRA* mutation is present (Liegl-Atzwanger et al. 2010; Kaemmer et al. 2009). *PDGFRA* mutations occur on either exon 18 or exon 14 (7%) and rarely on exon 12 (<1%). In adults, characteristics of *PDGFRA* mutated GISTs include presentation in the stomach and omentum, the appearance of epithelioid morphology, and an association with a benign clinical course (Liegl-Atzwanger et al. 2010).

No more than 10% of pediatric GIST patients display an oncogenic *KIT* mutation, and only two patients have displayed a *PDGFRA* mutation to date. The upregulation of fibroblast growth factor 4 (FGF 4), brain and acute leukemia, cytoplasmic (BAALC), insulin-like growth factor 1 (IGFR1), among others, has been reported in pediatric GIST (Benesch et al. 2009).

The immunohistochemical pattern of pediatric GIST is similar to that of adult GIST as it stains positive for CD117 (c-kit) (>95%) (Fig. 29.4); CD34 (70%); muscle markers including smooth muscle actin, calponin, and caldesmon (30%); and very rarely desmin and S100 (Benesch et al. 2009; Kaemmer et al. 2009; Machairas et al. 2010). Cytokeratins 8 and 18 are expressed in only a small percentage of GISTs while nestin, which is found in other mesenchymal tumors and schwannomas, is expressed in the majority of GISTs (Machairas et al. 2010). A road map pertaining to the diagnosis and treatment of GIST is presented in Fig. 29.5.

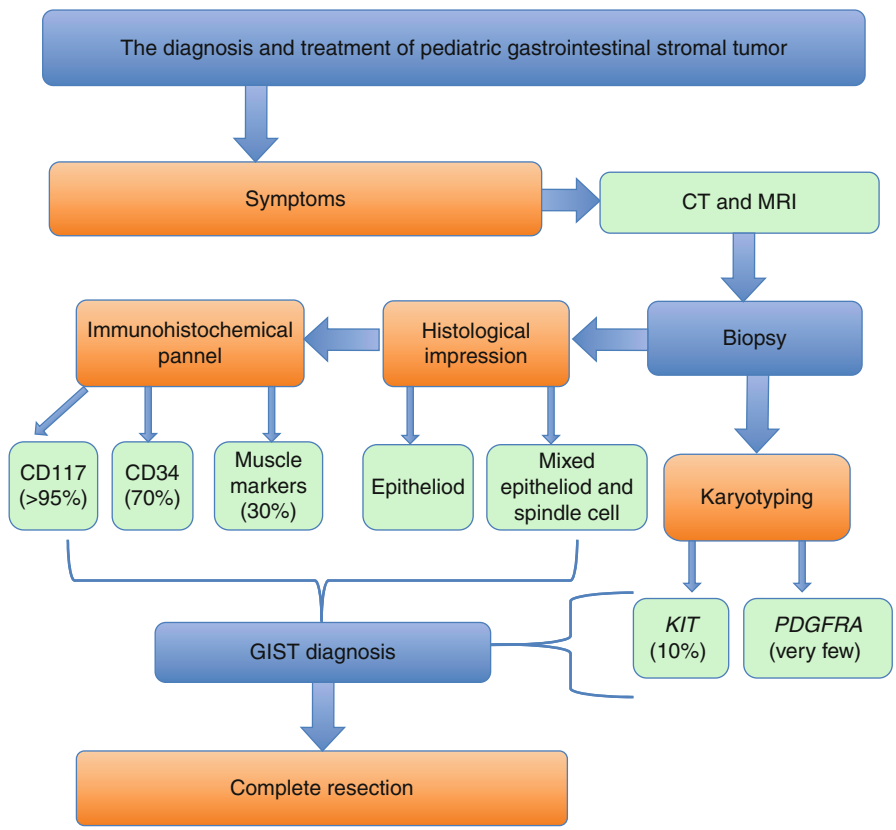

Fig. 29.5 Road map outlining the diagnosis and treatment of pediatric GIST

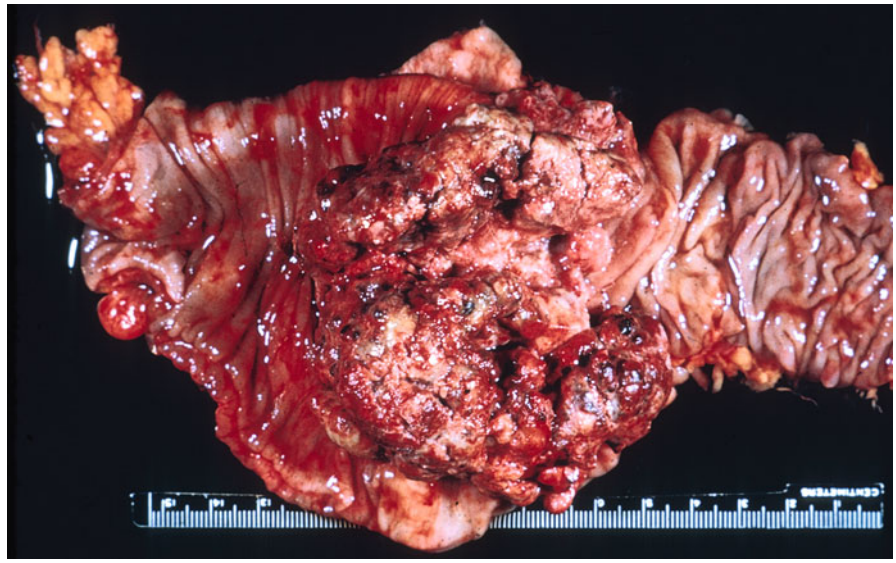

Fig. 29.6 Colon with invasive adenocarcinoma

29.3 Gastrointestinal Autonomic Nerve Tumors

Gastrointestinal autonomic nerve tumor (GANT) is a recently described variant of GIST. Required for the diagnosis of GANT is the absence of myogenic, schwann, and epithelial features (Kerr et al. 1999). They are also differentiated from GIST by showing neural differentiation using electron microscopy. While only a few cases of pediatric GANT have been reported, a slight predilection for females has been noted (Kerr et al. 1999; Benesch et al. 2009). In comparison to adult GANT, pediatric GANT tends to be smaller in size, is most commonly found in the stomach, and has a better prognosis. Pediatric GANT is typically treated using surgical resection (Kerr et al. 1999).

29.4 Colorectal Adenocarcinoma

Colorectal adenocarcinoma (CRAC) is the third most common malignancy in the adult population, surpassed by only lung and breast cancers (Sultan et al. 2010). An annual average of 9.4% of adult cancer cases and 7.9% of adult cancer deaths are attributed to CRAC, and therefore, it has been widely studied in this population. Pediatric CRAC, however, has not been extensively studied due to its rarity. Only one to two cases of CRAC per million children are reported annually (Sultan et al. 2010). The incidence of colorectal carcinoma in patients under 20 is on the rise (O'Connell et al. 2003). Sultan's investigation of the Surveillance, Epidemiology, and End Results database between 1986 and 1995 yielded 34 cases of colorectal carcinoma in patients <20 years of age; this figure nearly tripled to 94 between 1996 and 2005 (Sultan et al. 2010).

In adults, there is a slight predilection for males; however, this trend has not been reported in pediatric CRAC (Saab and Furman 2008). Patients, including those in younger age groups, typically present with abdominal pain, hematochezia, altered bowel habits, weight loss, and anemia. Pediatric patients often also complain of nausea, vomiting, abdominal distention, and abdominal mass. Acute abdominal conditions such as acute obstruction, perforation or severe pain mimicking appendicitis are also more common in children than in adults. The common occurrence of these symptoms in children may be attributed to their misdiagnosis until the mass reaches a large size. In children, the time from onset of symptoms to diagnoses is on average 3 months. This delay in diagnosis might be due to a combination of the rarity of CRAC in children and the symptomatic overlap with more common benign pediatric abdominal conditions (Saab and Furman 2008).

The pathology of CRAC is that of a malignant adenocarcinoma which often arise from polyps which undergo malignant degeneration (Fig. 29.6). In comparison to adults, where only 10–15% of tumors are

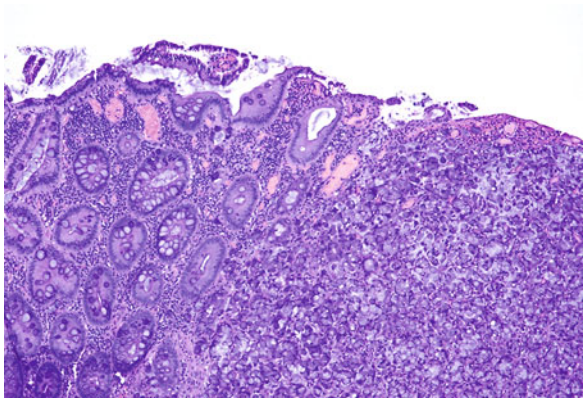

Fig. 29.7 Microscopic picture showing the transition from normal colonic mucosa to signet ring adenocarcinoma (100×)

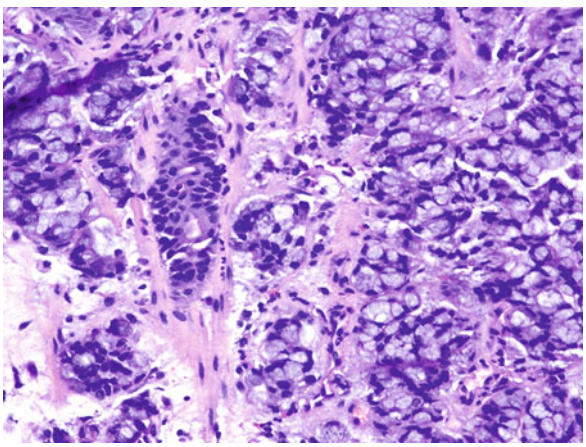

Fig. 29.8 Higher magnification of signet ring adenocarcinoma (400×)

of mucinous histology, pediatric CRACs have a high preponderance of mucinous lesions. More than 40% of tumors are signet cell carcinomas and poorly differentiated lesions (Figs. 29.7 and 29.8). The presence of this histology in adult CRAC is typically associated with an unfavorable outcome, yet due to the rarity of these tumors in children, the histological significance in this age group is unknown (Saab and Furman 2008).

A prognostic factor in adults, E-cadherin expression has not been studied in children with CRAC. Researchers have found that a decrease in E-cadherin expression in adults is an adverse prognostic indicator in several carcinomas, including esophageal, endometrial, ovarian, thyroid, and gastric (Lin et al. 2004; Mell et al. 2004; Brecelj et al. 2005; Faleiro-Rodrigues et al. 2005; Kim et al. 2009). Additionally, loss of E-cadherin is a characteristic of signet ring cell carcinoma, and it is surmised that this is an indicator for the more aggressive nature of such less differentiated colorectal carcinomas (Fig. 29.9) (Kim et al. 2002; Khoursheed et al. 2003; Borger et al. 2007). The author's current study shows no correlation between E-cadherin expression and the prognosis/staging of CRAC in children.

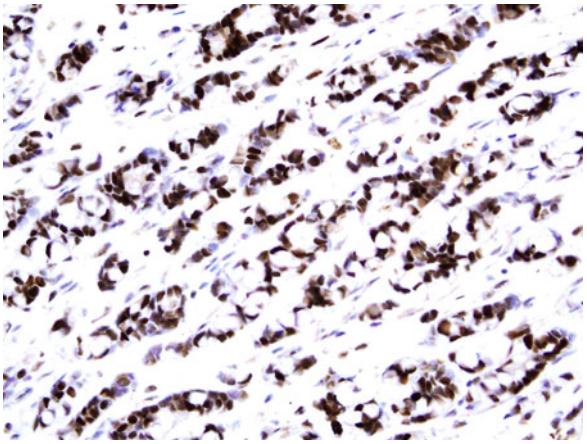

Fig. 29.9 Positive E-cadherin immunostain in signet ring adenocarcinoma

Adult CRAC staging guidelines based on surgery and pathology are typically used for children. The current staging system, developed by the American Joint Committee on Cancer, is based on the tumor pathology, lymph node involvement, margin infiltration, and occurrence of metastasis. Histologically, low-grade lesions (grade 1 and 2), which have no angiolymphatic invasion and no marginal involvement, are classified as favorable histology. If invasion is documented, total colonoscopy, complete blood count, blood chemistry panel with liver enzymes, and the carcinoembryonic antigen (CEA) level should be completed. While the CEA level in adults can help in the prediction of recurrence, the usefulness of this antigen in children remains unclear (Saab and Furman 2008). A road map pertaining to the diagnosis and treatment of CRAC is presented in Fig. 29.10.

There are three broad categories of pediatric CRAC: polyposis-associated CRAC, hereditary nonpolyposis colorectal cancer (HNPCC), and adenocarcinoma resulting from malignant degeneration of ulcerative colitis (UC). Polyposis-associated CRAC is linked with multiple familial polyposis syndromes including, familial adenomatous polyposis (FAP), MUTYH-associated

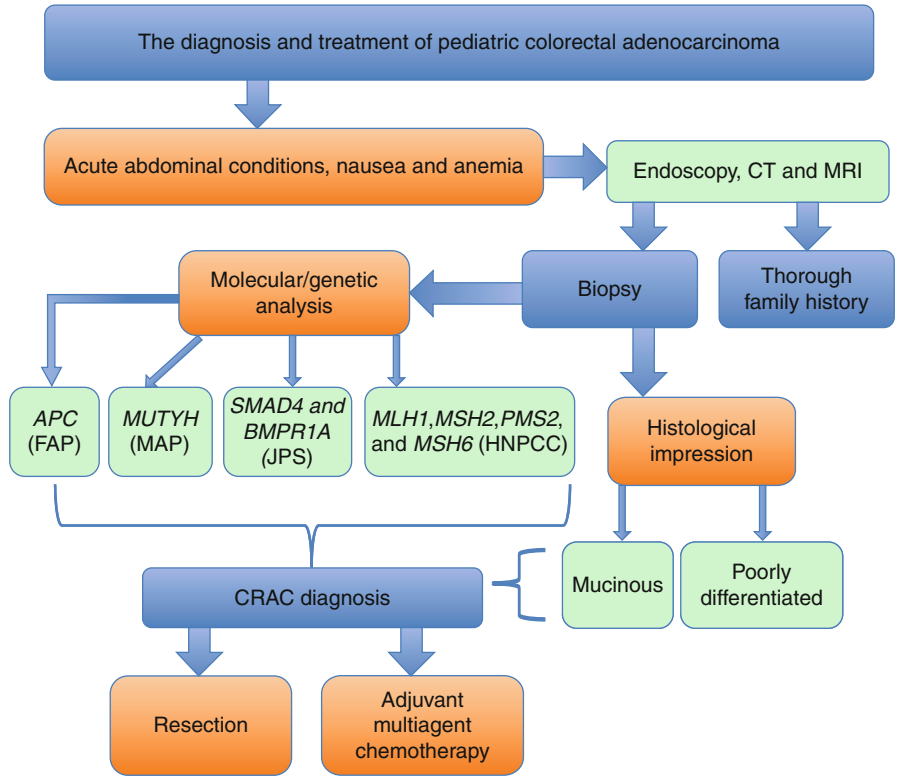

Fig. 29.10 Road map outlining the diagnosis and treatment of pediatric CRAC

polyposis syndrome (MAP), Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and juvenile hyerplastic polyposis syndrome (HPP) (Saab and Furman 2008). Peutz–Jeghers syndrome has not been reported in the pediatric population so it will not be further discussed.

Familial adenomatous polyposis is an autosomal dominant disorder with a 100% incidence rate of CRAC. Indicated in the etiology of this disorder is an inactivating germline mutation in 5q21, the adenomatous polyposis coli (*APC)* tumor suppressor gene. Acquired mutations of this gene are found in most sporadic cases of CRACs, and the youngest reported patient with FAB-associated CRAC was 5 years of age (Durno and Gallinger 2006; Saab and Furman 2008; Jasperson et al. 2010). MUTYH-associated polyposis syndrome, an autosomal recessive disorder, stems from a biallelic mutation in the *MUTYH* gene. According to Durno et al., only one pediatric patient (21 years of age) has had MAP-associated CRAC; however, they note that testing for this genetic mutation has not widely been performed in the pediatric population (Durno and Gallinger 2006; Jasperson et al. 2010). Juvenile polyposis syndrome is an autosomal dominant disorder with suggested germline inactivation mutations in *SMAD4* and *BMPR1A*. In patients under 35 years of age with JPS, there is a 15% incidence of CRAC (Saab and Furman 2008; Jasperson et al. 2010). Finally, the etiology of HPP is unknown (Jasperson et al. 2010).

An autosomal dominant condition, HNPCC or Lynch syndrome, accounts for roughly 3% of CRACs (Lynch, Lynch et al. 2009). Patients with Lynch syndrome have an increased risk of developing extracolonic cancers including those of the endometrium (~40%), stomach (~15%), ovary (~10%), hepatobiliary tract and pancreas (~5%), urinary tract (~4%), small bowel (~3%), and CNS (~2%) (Lagerstedt Robinson et al. 2007; Jang and Chung 2010). In comparison to patients with sporadic CRAC, those with HNPCC-related CRAC are often present at a lower stage, have lower incidence of metastases, and have more favorable prognosis (Saab and Furman 2008).

The biological basis of Lynch syndrome has been widely studied. Heterozygous germline mutations in four specific DNA mismatch repair (MMR) genes: *MLH1*, *MSH2*, *PMS2*, and *MSH6* have been linked with this disorder (5, 6). These genes are responsible for fixing sequencing errors that arise during DNA replication; therefore, if they become impaired, genetic errors may accumulate and, ultimately, carcinoma may occur. The accumulation of errors during DNA replication can occasionally lead to microsatellite instability (MSI), which is defined as erroneously lengthened or shortened repetitive DNA sequences. Most Lynch syndrome patients display MSI; however, it can also occur in up to 15% of CRACs unrelated to Lynch syndrome. In non-HNPCC patients, MSI is typically due to acquired hypermethylation of the *MLH1* gene promoter (Lagerstedt Robinson et al. 2007; Boland and Goel 2010; Jang and Chung 2010). *MLH1* and *MSH2* gene mutations are seen in up to 90% of Lynch syndrome patients while *MSH6* and *PMS2* gene mutations constitute the remaining 10% of cases (Jasperson et al. 2010). The biallelic mutations of one of the MMR genes lead to a distinct phenotype that includes multiple adenomatous polyps and café au lait skin macules (Poley et al. 2007; Durno et al. 2010).

To ensure early diagnosis of this rare disease, strict diagnostic criteria (the Amsterdam criteria) were created in 1990 with the hopes of improving morbidity and mortality rates. Since its inception, modifications have been made to include other HNPCC-related cancers (Amsterdam II criteria). The diagnostic criteria of HNPCC require the patient to have: (1) three or more family members with colorectal carcinoma where one is a first-degree relative of another, (2) two successive affected generations, and (3) the diagnosis of an HNPCC-related cancer relative before 50 years of age (Lynch et al. 2009).

Due to the rarity of CRAC in the pediatric population, routine workup should include a thorough family history and pending results, genetic testing performed (Davidson 2007; Jasperson et al. 2010). While FAP, JPS, and Peutz–Jeghers syndrome predispose patients to the formation of multiple polyps, Lynch syndrome – the most common genetic abnormalities associated with CRAC – does not, and therefore, patients with this syndrome require a higher level of clinical suspicion (Jasperson et al. 2010). If a patient is suspected of having HNPCC, genetic tests for MMR genes and immunohistochemical stains that demonstrate the absence of the protein that corresponds to the aberrant gene are available (Lynch et al. 2009). Immunohistochemical staining for microsatellite instability may also be performed in cases suspicious for HNPCC with excessive mucin or poorly differentiated signet ring cells (Jass 2007).

Behind FAP and Lynch syndrome, ulcerative colitis is the third highest condition at risk for CRAC. The development of CRAC in UC patients is mainly related to longstanding chronic inflammation of the bowel, and the longer symptoms of UC persist, the greater the chances that CRAC will occur. One study found that the presence of UC increases the risk of CRAC by 19-fold compared to the general population. When associated with UC, CRAC develops in the affected mucosa and in areas proximal to gross colitis. When UC is found in the pediatric population, the risk of CRAC is heightened (Saab and Furman 2008; Kulaylat and Dayton 2010). One report noted that children who have UC for more than 5 years are more prone to develop CRAC, whereas in the adult population, this risk does not increase until after 10 years (Saab and Furman 2008). The subtypes most often observed of UC-associated CRAC are mucinous or signet cell, and multiple lesions are typically found. Surveillance measures include regular colonoscopies as well as random serial biopsies (Kulaylat and Dayton 2010).

29.4.1 Cancer of the Stomach

Adenocarcinomas account for 95% of gastric cancers. They are extremely rare in children and adolescents (Schwartz and Sgaglione 1984). The differential diagnosis includes: GIST, lymphomas, squamous cell carcinomas, carcinoids, and leiomyosarcoma (Fig. 29.1).

29.4.2 Cancer of the Pancreas

Pancreatic cancer is a frequent cause of death from cancer in adults. Pancreatic tumors are extremely rare in children and adolescents (Dall'igna et al. 2010; Chung et al. 2006). Pancreatic cancers present variable histologies that include: papillary-cystic carcinomas, adenocarcinomas, squamous cell carcinomas, acinic cell carcinomas, liposarcomas, pancreatoblastomas, glucagonomas, gastrinomas, and malignant insulinomas (Vossen et al. 1998; Shorter et al. 2002; Raffel et al. 2004). Primitive neuroectodermal tumors and lymphomas have also

been reported (Movahedi-Lankarani et al. 2002). Many of these tumors do not produce hormones. Pancreatic carcinoma and pancreatoblastoma can produce hormones and may be associated with wasting and pain (Murakami et al. 1996; Schwartz 1997; Imamura et al. 1998). Pancreatoblastoma has been associated with Cushing syndrome and Beckwith–Wiedemann syndrome (Muguerza et al. 2005). Complete resection is the mainstay of treatment. Solid pseudopapillary neoplasm of the pancreas has been reported in children. It has been called a "borderline" malignancy. It is also treated with surgical excision. AFP elevation has also been reported in pancreatoblastoma (Dhebri et al. 2004).

29.4.3 Carcinoid Tumor

Carcinoid tumors are rare in children but may be located in the esophagus and bronchi in the thorax. In the abdomen, they occur in the pancreas and small and large bowel, including the appendix. Many are found after appendectomy. Tumors of appendix are usually benign. Tumors contain argentaffin granules which are thought to arise from small intestine Kulchitsky cells. These cells may secrete proteins, such as somatostatin, leading to the clinical symptoms of carcinoid syndrome.

29.4.4 Cancer of the Bladder, Cervix, and Vagina

Bladder carcinomas are extremely rare in children. Most pediatric bladder carcinomas are low grade, in contrast to similar tumors in adults. Papillary urothelial neoplasm of low malignant potential (PUNLUP) may be the most common entity in children (Alanee and Shukla 2010). Most of these tumors are superficial and easily treated

Table 29.1 Overview of Rare pediatric abdominal tumors

Tumor type	Adrenocortical tumors	Gastric tumors	Pancreatic tumors
Classification	• Ademona • Carcinoma	• Epithelioid leiomyoma • Leiomoyosarcoma • Carcinoid • Non-Hodgkin lymphoma	• Papillary-cystic carcinoma • Pancreatoblastoma • Acinic cell carcinoma • Malignant insulinoma • Glucagonoma • Gastrinoma • PNET • Lymphoma
Associated syndrome	• Li–Fraumeni syndrome • Beckwith–Wiedemann syndrome • Hemihypertrophy	• Epithelioid leiomyoma and leiomyosarcoma: Carney's triad	• Pancreatoblastoma: Beckwith–Weidemann syndrome and Cushing syndrome
Metastasis	• Lymph node • Kidney • Lung • Bone • Brain	N/A	• Direct invasion of liver
Treatment	• Surgical removal • Hormone therapy • Chemotherapy	• Surgical removal • Radiation therapy • Chemotherapy	• Surgical removal: partial or complete pancreatectomy • Chemotherapy
Prognosis	• Excellent: small resectable tumors • Fair: large primary tumors or metastatic disease at diagnosis	• Dependent on extent of disease and treatment success; no comprehensive studies	• Good: complete surgical resection • Poor: pancreatoblastoma

Rare tumors of the liver such as undifferentiated embryonal sarcoma are not included in this table as they are mentioned in the liver chapter

PNET primitive neuroectodermal tumor

with surgery. Squamous cell carcinomas do occur in children (Sung and Koyle 2000; Lezama-del Valle et al. 2004). In pediatric cancer survivors, there is an association between the development of bladder carcinoma and treatment with alkylating agents, such as cyclophosphamide (Johansson and Cohen 1997). Adenocarcinoma of cervix and vagina are extremely rare in children and adolescents (McNall et al. 2004). The median age of presentation is 15 years, and two-thirds are associated with exposure to diethylstilbestrol in utero. These tumors tend to present at higher stage III or IV in these adolescents. This may be because this population is not routinely examined with routine PAP smears.

References

Alanee S, Shukla AR (2010) Bladder malignancies in children aged <18 years: results from the Surveillance, Epidemiology and End Results database. BJU Int 106(4):557–560

Benesch M, Wardelmann E et al (2009) Gastrointestinal stromal tumors (GIST) in children and adolescents: a comprehensive review of the current literature. Pediatr Blood Cancer 53(7):1171–1179

Boland CR, Goel A (2010) Microsatellite instability in colorectal cancer. Gastroenterology 138(6):2073–2087.e3

Borger ME, Gosens MJ et al (2007) Signet ring cell differentiation in mucinous colorectal carcinoma. J Pathol 212(3):278–286

Brecelj E, Frkovic Grazio S et al (2005) Prognostic value of E-cadherin expression in thyroid follicular carcinoma. Eur J Surg Oncol 31(5):544–548

Chung EM, Travis MD et al (2006) Pancreatic tumors in children: radiologic-pathologic correlation. Radiographics 26(4):1211–1238

Dall'igna P, Cecchetto G et al (2010) Pancreatic tumors in children and adolescents: the Italian TREP project experience. Pediatr Blood Cancer 54(5):675–680

Davidson NO (2007) Genetic testing in colorectal cancer: who, when, how and why. Keio J Med 56(1):14–20

Dhebri AR, Connor S et al (2004) Diagnosis, treatment and outcome of pancreatoblastoma. Pancreatology 4(5):441–451; discussion 452–453

Durno CA, Gallinger S (2006) Genetic predisposition to colorectal cancer: new pieces in the pediatric puzzle. J Pediatr Gastroenterol Nutr 43(1):5–15

Durno CA, Holter S et al (2010) The gastrointestinal phenotype of germline biallelic mismatch repair gene mutations. Am J Gastroenterol 105(11):2449–2456

Faleiro-Rodrigues C, Macedo-Pinto IM et al (2005) Biological relevance of E-cadherin-catenin complex proteins in primary epithelial ovarian tumours. Gynecol Obstet Invest 60(2):75–83

Imamura A, Nakagawa A et al (1998) Pancreatoblastoma in an adolescent girl: case report and review of 26 Japanese cases. Eur J Surg 164(4):309–312

Jang E, Chung DC (2010) Hereditary colon cancer: lynch syndrome. Gut Liver 4(2):151–160

Jasperson KW, Tuohy TM et al (2010) Hereditary and familial colon cancer. Gastroenterology 138(6):2044–2058

Jass JR (2007) Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 50(1):113–130

Johansson SL, Cohen SM (1997) Epidemiology and etiology of bladder cancer. Semin Surg Oncol 13(5):291–298

Kaemmer DA, Otto J et al (2009) The Gist of literature on pediatric GIST: review of clinical presentation. J Pediatr Hematol Oncol 31(2):108–112

Kerr JZ, Hicks MJ et al (1999) Gastrointestinal autonomic nerve tumors in the pediatric population: a report of four cases and a review of the literature. Cancer 85(1):220–230

Khoursheed MA, Mathew TC et al (2003) Expression of E-cadherin in human colorectal cancer. Surgeon 1(2):86–91

Kim HC, Kim HJ et al (2002) Reduced E-cadherin expression as a cause of distinctive signet-ring cell variant in colorectal carcinoma. J Korean Med Sci 17(1):23–28

Kim MA, Lee HS et al (2009) Prognostic importance of epithelial-mesenchymal transition-related protein expression in gastric carcinoma. Histopathology 54(4):442–451

Kulaylat MN, Dayton MT (2010) Ulcerative colitis and cancer. J Surg Oncol 101(8):706–712

Lagerstedt Robinson K, Liu T et al (2007) Lynch syndrome (hereditary nonpolyposis colorectal cancer) diagnostics. J Natl Cancer Inst 99(4):291–299

Lezama-del Valle P, Jerkins GR et al (2004) Aggressive bladder carcinoma in a child. Pediatr Blood Cancer 43(3):285–288

Liegl-Atzwanger B, Fletcher JA et al (2010) Gastrointestinal stromal tumors. Virchows Arch 456(2):111–127

Lin YC, Wu MY et al (2004) Prognostic and clinicopathological features of E-cadherin, alpha-catenin, beta-catenin, gamma-catenin and cyclin D1 expression in human esophageal squamous cell carcinoma. World J Gastroenterol 10(22): 3235–3239

Lynch HT, Lynch PM et al (2009) Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet 76(1):1–18

Machairas A, Karamitopoulou E et al (2010) Gastrointestinal stromal tumors (GISTs): an updated experience. Dig Dis Sci 55(12):3315–3327

McNall RY, Nowicki PD et al (2004) Adenocarcinoma of the cervix and vagina in pediatric patients. Pediatr Blood Cancer 43(3):289–294

Mell LK, Meyer JJ et al (2004) Prognostic significance of E-cadherin protein expression in pathological stage I–III endometrial cancer. Clin Cancer Res 10(16):5546–5553

Movahedi-Lankarani S, Hruban RH et al (2002) Primitive neuroectodermal tumors of the pancreas: a report of seven cases of a rare neoplasm. Am J Surg Pathol 26(8):1040–1047

Muguerza R, Rodriguez A et al (2005) Pancreatoblastoma associated with incomplete Beckwith-Wiedemann syndrome: case report and review of the literature. J Pediatr Surg 40(8):1341–1344

Murakami T, Ueki K et al (1996) Pancreatoblastoma: case report and review of treatment in the literature. Med Pediatr Oncol 27(3):193–197

O'Connell JB, Maggard MA et al (2003) Rates of colon and rectal cancers are increasing in young adults. Am Surg 69(10):866–872

Poley JW, Wagner A et al (2007) Biallelic germline mutations of mismatch-repair genes: a possible cause for multiple pediatric malignancies. Cancer 109(11):2349–2356

Raffel A, Cupisti K et al (2004) Therapeutic strategy of papillary cystic and solid neoplasm (PCSN): a rare non-endocrine tumor of the pancreas in children. Surg Oncol 13(1): 1–6

Saab R, Furman WL (2008) Epidemiology and management options for colorectal cancer in children. Paediatr Drugs 10(3):177–192

Schwartz MZ (1997) Unusual peptide-secreting tumors in adolescents and children. Semin Pediatr Surg 6(3):141–146

Schwartz MG, Sgaglione NA (1984) Gastric carcinoma in the young: overview of the literature. Mt Sinai J Med 51(6):720–723

Shimomura M, Ikeda S et al (2010) Gastrointestinal stromal tumors of the small intestine in pediatric populations: a case report and literature review. Pediatr Surg Int 26(6):649–654

Shorter NA, Glick RD et al (2002) Malignant pancreatic tumors in childhood and adolescence: the Memorial Sloan-Kettering experience, 1967 to present. J Pediatr Surg 37(6):887–892

Sultan I, Rodriguez-Galindo C et al (2010) Distinct features of colorectal cancer in children and adolescents: a population-based study of 159 cases. Cancer 116(3):758–765

Sung JD, Koyle MA (2000) Squamous cell carcinoma of the bladder in a pediatric patient. J Pediatr Surg 35(12): 1838–1839

Vossen S, Goretzki PE et al (1998) Therapeutic management of rare malignant pancreatic tumors in children. World J Surg 22(8):879–882

Gastrointestinal Cancer Predisposition Syndromes

30

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Contents

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Gastrointestinal cancer is extremely rare in children and adolescents. The etiology in most cases is due to familial syndromes (Saab and Furman 2008).

The two best characterized familial syndromes, hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), are autosomal dominant inherited disorders accounting for approximately 2% and 0.1–1% of all adult cases of colorectal carcinomas, respectively. But also other polyposis syndromes affect children: Peutz–Jeghers syndrome and juvenile polyposis coli. All these syndromes rarely cause malignant colorectal tumors in young carriers, however, extracolonic manifestations and preneoplastic lesions must be considered and often occur in pediatric patients.

30.1 Adenomatous Polyposis Syndrome (FAP)

Familial Adenomatous Polyposis (FAP, OMIM N175100) is a dominantly inherited colorectal cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps (adenomas) and extracolonic manifestations and/or neoplasms (tumors) are variably present.

FAP is generally caused by germline inactivating mutations in the Adenomatous Polyposis Coli gene (APC) at 5q21, which encodes a protein of 2,843 aminoacids (Vasen et al. 2008). APC is a tumor suppressor gene, member of the WNT pathway. Normally, the WNT pathway leads to changes in gene expression profile; in fact, APC is able to form a multiprotein complex with glycogen synthesis kinase-3ß and axin, and to bind ß-catenin, which in turn is phosphorylated

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by glycogen synthase kinase-3ß and subsequently degraded by the proteasome. If APC is mutated, the multiprotein complex could not be formed and, therefore, ß-catenin accumulates into the cytoplasm and then translocates to the nucleus, where it activates the T-cell factor, which in turn causes transcription of target genes, influencing different cellular processes such as cell migration, cell cycle control, differentiation, and apoptosis (Kundu et al. 2006).

APC gene is considered at high penetrance activity so, patients carrying a germline mutation, have theoretically the 100% of risk to develop at early age a colorectal cancer if not adequately treated.

The standard prophylactic approach is still surgical. Generally a total colectomy (extended to the rectum in specific pathological conditions) is required to interrupt the sequence from adenoma to cancer, and the frequent endoscopic screening of the individuals at risk is mandatory from the age of 10–14 years. However, it is imperative to have the best risk estimation and to submit to endoscopy, only individuals that with high probability could develop colorectal lesions, as indicated in the main International Guidelines (Vasen et al. 2008).

FAP affects about 1 in 7,000 individuals. Two types of FAP exist, and a relationship between the location of mutations in the gene and the phenotypic expression of FAP has been established (Vasen et al. 2008; Signoroni et al. 2010): the sparse or attenuated type (generally defined as AFAP) is characterized by hundreds of polyps, and the profuse type presents with thousands of polyps (Fig. 30.1). In general adenomas tend to develop near puberty, although early childhood presentations can occur.

Another polyposis-causing gene was detected on chromosome 1p33-34, the MUTYH gene (OMIM n. 608456). Mutations in this gene have been found to be associated with a milder form of polyposis named MAP. MUTYH germline mutations are related to an attenuated phenotype and have been reported in 10–30% of patients without an APC mutation. For these reasons, it could be considered another important biomarker in identifying polyposis and in particular attenuated phenotype patients. Recent studies have also demonstrated that germline MUTYH mutations predispose to colorectal cancer with an autosomal recessive pattern, accounting for up to 1% of these neoplasms. In this setting, biallelic MUTYH mutations have been found to be associated with a 93-fold excess risk of colorectal cancer, with almost complete penetrance by 60 years of age. Interestingly, in up to one-third of these patients, no associated adenoma was found (Vasen et al. 2008; Kundu et al. 2006; Signoroni et al. 2010; Al-Sukhni et al. 2008). In contrast, the influence

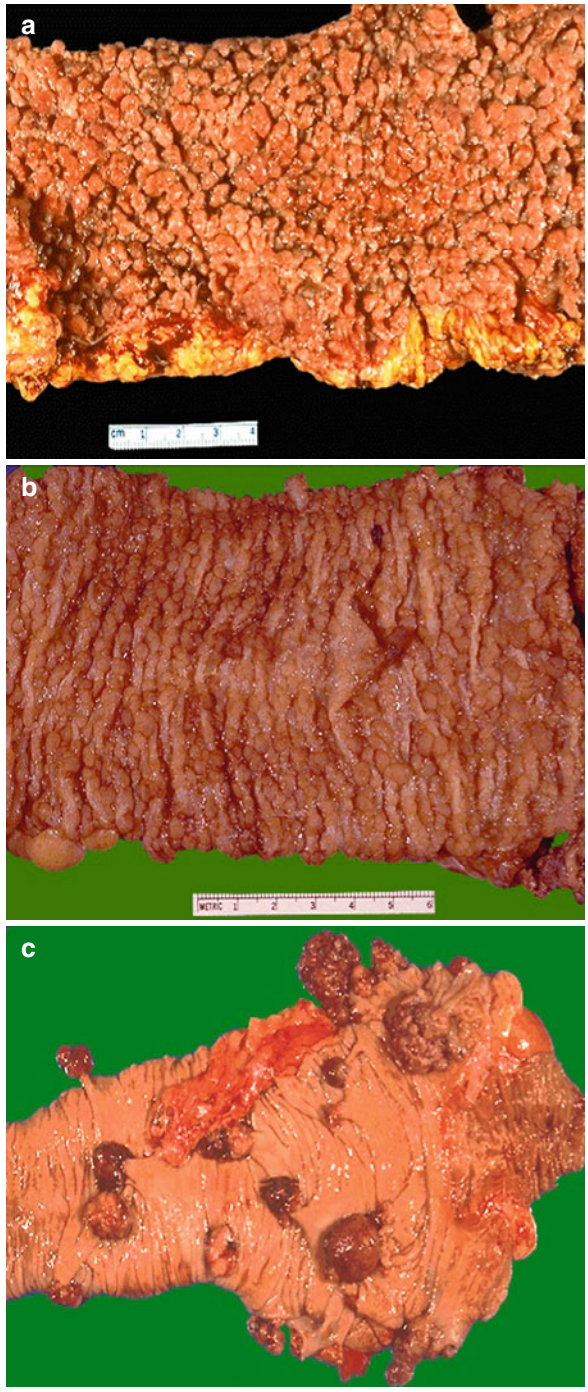

Fig. 30.1 The variability of FAP phenotype: (**a**) severe polyposis, (**b**) classical polyposis, (**c**) attenuated polyposis

of monoallelic MYH mutations on colorectal risk remains controversial, although recent studies suggest a modest effect (Jenkins et al. 2006). The MUTYH gene encodes a member of the base excision repair system. This system is composed of three enzymes (MYH, OGG1, and MTH1) that contribute to protect cells against the mutagenic effects of aerobic metabolism. MUTYH is a DNA glycosylase, which acts at a third level of defense, and is responsible for the removal of adenines mispaired with 8-oxoguanine, one of the most mutagenic DNA products of oxidative DNA damage. Failure to correct these mispairs leads to somatic G:C→T:A transversions in target genes, namely, APC and KRAS. Somatic G:C→T:A transversions in the APC gene were described and in addition, G:C→T:A transversions in the KRAS gene were also observed in adenomas from AFAP patients (David et al. 2007).

Although MAP patients have milder disease, starting later in life, it should be considered that colorectal cancer was frequently found in these subjects and so they need strict surveillance programs like classical FAP patients, to reduce risk of developing cancer. Some reports have identified cases of upper gastrointestinal adenomas/polyps also in MAP patients, so also the upper gastrointestinal tract needs controls (Bouguen et al. 2007).

The gastrointestinal tract is also affected in FAP: duodenal, particularly water papilla and gastric polyps seem to be an important and typical manifestation of FAP patients, but generally related to an adult age.

FAP is also associated with the development of extracolonic malignancies including thyroid carcinoma and hepatoblastoma. Clinical phenotype, including the presence of extracolonic abnormalities, appears to vary according to the site of the APC gene mutation and the presentation of modifying genes. After a diagnosis is made, annual sigmoidoscopy is recommended starting about 10 years of age (Table 30.1). As soon as polyps are identified, prophylactic colectomy can be considered at 15 years of age unless suspicious lesions are found earlier (Signoroni et al. 2010).

Two variants of FAP, with the same propensity to progress to CRC and extraintestinal disease manifestations must be considered. One is Gardner syndrome in which FAP is associated with desmoids tumors, epidermoid cysts, fibromas, osteomas, and congenital hypertrophy of the retinal pigment epithelium. Patients with Gardner syndrome are at high risk to develop a desmoid tumor of the abdominal wall or mesentery after colectomy, which can then be a leading cause of morbidity and mortality (Saab and Furman 2008; Vasen et al. 2008; Signoroni et al. 2010).

Table 30.1 Colorectal surveillance protocol in family member at risk for (A) FAP

	Type of investigation	Lower age limit	Interval
Classical FAP	Sigmoidoscopy[a]	10–12 years	2 years[a]
AFAP	Colonoscopy	18–20 years	2 years[a]

From Vasen et al. (2008)
(A)FAP (attenuated) familial adenomatous polyposis
[a]Once adenomas are detected annual colonoscopy should be performed until colectomy is planned

Turcot syndrome is another FAP variant that includes multiple pediatric brain tumors (medulloblastoma, glioma, and ependymoma) in conjunction with FAP (Saab and Furman 2008; Vasen et al. 2008; Signoroni et al. 2010).

30.2 Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes are a rare group of hereditary autosomal dominant disorders that comprise less than 1% of all hereditary colorectal cancers (Manfredi 2010). Hamartomatous polyps, in and of themselves, are benign entities; however, these hamartomatous polyposis syndromes have a malignant potential for the development of colorectal cancer as well as extracolonic cancers. Early detection and proper surveillance are vital to minimize the risk of carcinoma.

The hamartomatous polyposis syndromes include juvenile polyposis syndrome (JPS); PTEN hamartoma tumor syndrome, which includes Cowden syndrome (CS) and Bannayan–Riley–Ruvalcaba syndrome (BRRS); and Peutz–Jeghers syndrome (PJS) (Manfredi 2010).

30.2.1 Juvenile Polyposis Syndrome

Juvenile polyps are the most common type of pediatric gastrointestinal polyps. Solitary juvenile polyps can develop at any age, though they appear most frequently in preschool children and have an incidence of 2% in children under 10 years of age. Solitary polyps are

Table 30.2 Juvenile[a] polyposis syndrome (JPS) is diagnosed if at least one of the following clinical criteria is present

Criteria
More than five juvenile polyps of the colorectum
Multiple juvenile polyps of the upper and lower GI tract
Any number of juvenile polyps and a family history of juvenile polyps

[a]The term "juvenile" refers to the type of polyp not the age of onset of polyps. Juvenile polyps are hamartomas that develop from an abnormal collection of tissue elements normally present at this site

generally located in the rectosigmoid area and are usually considered to be a separate entity from JPS, which has an incidence of 1 in 100,000–160,000 individuals (Chow and Macrae 2005). A family history of juvenile polyps is found in 20–50% of patients with JPS, with an autosomal dominant inheritance pattern of variable penetrance (Chow and Macrae 2005; Attard and Young 2006).

The diagnosis of JPS is clinically established based upon the presence of at least 1 of the following criteria (Jass et al. 1988; Giardiello et al. 1991): more than five polyps detected on colonoscopy; polyps located outside of the colon; and any number of polyps in a patient with a family history of juvenile polyps (Table 30.2).

The gross appearance of a juvenile polyp is spherical to slightly lobular in shape, and most are pedunculated with long stalks (Horrilleno et al. 1957). In patients with JPS, polyps may have a multilobulated appearance of a villiform or papillary shape (Desai et al. 1995). Jass and colleagues reported that approximately 20% of polyps have the latter appearance (Jass et al. 1988). Polyp size can range from several millimeters to 3 cm. These polyps are typically very vascular, with a smooth and glistening appearance on the surface; however, they may also have an ulcerated surface from auto-infarction.

Three genes have been associated with JPS: *SMAD4*, *BMPR1A*, and *ENG*, all of which are part of the transforming growth factor-b(TGF-b) superfamily of proteins (18). The *PTEN* gene mutation in patients with juvenile polyposis is a controversial topic. It is generally thought that patients with the *PTEN* gene mutation likely represent CS or BRRS patients who have not yet expressed the extraintestinal clinical features of these conditions (Zbuk and Eng 2007).

Individuals with JPS are at risk for the development of colorectal, gastric, small intestinal, and pancreatic cancers. The risk of developing colorectal cancer from solitary juvenile polyps is thought to be negligible or nonexistent (Coburn et al. 1995). However, individuals with JPS are at risk for developing adenomatous change and carcinoma. The incidence of colorectal cancer has been reported by Jass and associates to be 20.7%, with a mean age of 34 years (age range, 15–59 years) and an estimated cumulative colorectal cancer risk of 68% by 60 years of age (Jass et al. 1988).

30.2.2 PTEN Hamartoma Tumor Syndrome: Cowden Syndrome and Bannayan–Riley–Ruvalcaba Syndrome

Cowden syndrome (CS) is a rare autosomal dominant syndrome, with a reported incidence of 1 in 200,000 individuals (Nelen et al. 1997). This syndrome is characterized by macrocephaly, mucocutaneous lesions (such as facial trichilemmoma), acral keratosis, and papillomatous papules. It is also associated with thyroid, breast, and endometrial manifestations, including cancer in all of these areas (Zbuk and Eng 2007; Calva and Howe 2008; Starink et al. 1986). CS has been linked to Lhermitte–Duclos disease, which is characterized by hamartomas of the cerebellum (Albrecht et al. 1992). Hamartomatous polyps throughout the gastrointestinal tract are associated with this syndrome but are not as common as the extraintestinal findings associated with the syndrome. The incidence of gastrointestinal polyps in CS varies in the literature, ranging anywhere from 30% (Starink et al. 1986; Eng 2000). It is generally thought that the incidence of gastrointestinal polyps in CS is less than that of BRRS, though this belief is debated in the literature (Eng 2000). Another gastrointestinal manifestation of CS is glycogenic acanthosis of the esophagus, which involves large benign glycogen-filled epithelial cells that are gray to white in color (McGarrity et al. 2003).

The Bannayan–Riley–Ruvalcaba Syndrome (BRRS) is characterized by macrocephaly, developmental delays, pigmented speckling of the penis, lipomas, and hamartomatous polyps of the intestine (Gorlin et al. 1992). The incidence of gastrointestinal polyps in BRRS has been reported to be 45% (Gorlin et al. 1992).

CS and BRRS have an autosomal dominant inheritance pattern with variable penetrance. Both syndromes have been associated with the *PTEN* gene, which is located on chromosome 10q22–23 (Eng and Ji 1998).

The *PTEN* gene is a tumor suppressor gene that is also a tyrosine phosphatase that dephosphorylates tyrosine, serine, and threonine (Suzuki et al. 1998). PTEN is a negative regulator of the Akt/PKB signaling pathway (Suzuki et al. 1998; Waite and Eng 2002), which controls the levels of phosphoinositol triphosphate. PTEN is also involved in regulating cell cycle, apoptosis, and angiogenesis (Waite and Eng 2002; Chow and Baker 2006).

Individuals with CS are at risk for developing breast, thyroid, and endometrial cancers. The risk of adenocarcinoma of the breast has been reported to range from 30% to 50% in women with CS (Zbuk and Eng 2007; Starink et al. 1986; Eng 2000). In addition, there are reports of breast cancer in men with CS (Fackenthal et al. 2001). Individuals with CS are also subject to benign conditions of the breast such as fibrocystic disease (Starink et al. 1986). Thyroid abnormalities such as multinodular goiter and thyroglossal duct cysts are associated with this syndrome, as well as a 10% risk of thyroid cancer. CS patients also have a risk of leiomyomas, as well as an up-to-10% risk of endometrial cancer (Starink et al. 1986). Renal cell cancer has also been associated with CS (Starink et al. 1986). The risk of developing gastrointestinal carcinoma in CS is unclear at this point. It has been reported by some studies that there is no increased risk of gastrointestinal cancer; however, there are multiple case reports of gastric and colorectal cancer (Starink et al. 1986; Carlson et al. 1984).

In BRRS, the cancer risk is unclear. The limited number of patients with this disease makes it difficult to determine the risk; however, there have been case reports of breast and endometrial cancer (Marsh et al. 1999; Longy et al. 1998). With additional evidence supporting the idea that CS and BRRS are variable phenotypic expressions in the *PTEN* gene, it is therefore recommended that individuals with BRRS be considered at risk for malignancy, as with CS.

30.2.3 Peutz–Jeghers Syndrome

PJS, as with the other hamartomatous syndromes, is an autosomal dominant syndrome that is typified by its characteristic mucocutaneous pigmentation and intestinal hamartomatous polyps. The incidence of PJS is reported to be 1 in 150,000–200,000 individuals (Boardman 2002; Kutscher et al. 1960). Pigmentation

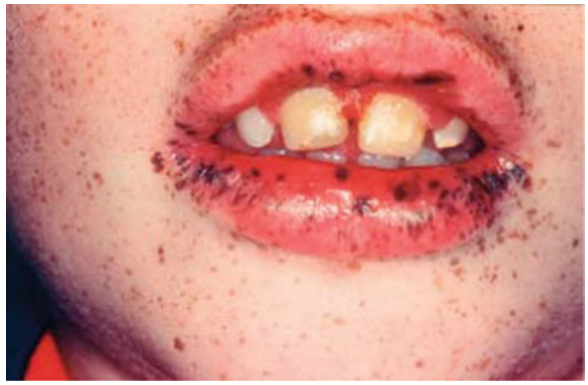

Fig. 30.2 Mucocutaneous pigmentation around lips in Peutz–Jeghers syndrome

is seen around the vermilion border of the lips in over 95% of cases, with the buccal mucosa being the second most common site (80%) (Traboulsi and Maumenee 1986; Utsunomiya et al. 1975) (Fig. 30.2). Other areas of pigmentation include the hands, feet, genitals, and around the nose and eyes. Pigmentation typically presents in early childhood and starts to fade with age usually after the start of puberty (Giardiello and Trimbath 2006).

Hamartomatous polyps in PJS are commonly found in the small intestine; however, they are also found in the stomach and colon. The number of polyps in the intestine may range from 1 to a complete carpeting of the gastrointestinal tract (Utsunomiya et al. 1975; Westerman and Wilson 1999). The most common presentation of PJS is abdominal pain secondary to intussusception. Other clinical presentations include anemia, melena, hematochezia, hematemesis, and obstruction. Approximately one-third of PJS patients present in the first decade of life, with up to 60% presenting by the second or third decade (Giardiello and Trimbath 2006; Brosens et al. 2007).

The diagnosis of PJS is clinically established on the presence of histologic tissue that is consistent with hamartomatous polyps and two of the following criteria (Giardiello et al. 1987): a family history of PJS; the presence of mucocutaneous pigmentation and the presence of small-bowel polyps.

PJS, as with the other hamartomatous syndromes, has an autosomal dominant pattern of inheritance with both familial and sporadic transmission. The gene associated with PJS is a serine-threonine kinase that is located on chromosome 19p13.3 (Hemminki et al. 1997;

Mehenni et al. 1997). Hemminki and coworkers and Jenne and associates independently identified the gene in this region as *LKB1/STK11* (Hemminki et al. 1998; Jenne et al. 1998). This gene has been reported in 80% of patients with PJS. Common mutations are frameshift and nonsense mutations in exons 1–6; however, large deletion mutations missed by direct sequencing have been recently described using multiple ligation probes (Volikos et al. 2006).

LKB1/STK11 is a tumor suppressor gene that encodes a serine-threonine kinase that phosphorylates and activates members of the AMPK-related subfamily of protein kinases (Forcet et al. 2005). LKB1/STK11 has an essential role in G1 cell cycle arrest, cell polarity, p53-dependent apoptosis, and cellular energy levels (Forcet and Billaud 2007; Marignani 2005). *LKB1* (+/–) mice develop gastrointestinal polyps with histologic characteristics resembling those of human PJS polyps (Miyoshi et al. 2002).

Individuals with PJS are at risk for the development of colorectal, gastric, small intestinal, esophageal, and pancreatic cancers but generally not in pediatric age. PJS patients are also at risk for extraintestinal cancer such as lung, breast, ovarian, testicular, and endometrial cancers (Saab and Furman 2008; Zbuk and Eng 2007; Giardiello and Trimbath 2006). A meta-analysis showed that the risk of developing any type of cancer by 64 years of age was 93% (relative risk of 15) (giardiello et al. 2000).

30.3 Hereditary Non-polyposis Colorectal Cancer (HNPCC)

Hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome is a rare hereditary disease that accounts for about 1–5% of all colorectal cancers (Gryfe 2009). It is an autosomal dominant condition caused by the mutation of one of several DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, and PMS2, leading to microsatellite instability (MSI). The average age of colorectal cancer diagnosis in Lynch syndrome mutation carriers is 44 years, compared with 64 years in sporadic colorectal cancer. Individuals with a Lynch syndrome gene mutation have an estimated 80% lifetime risk of developing colorectal cancer. The identification of Lynch syndrome patients is fundamental to address them to correct intensive surveillance programs and to the right therapeutic strategies (Gryfe 2009).

The research criteria for defining Lynch syndrome were established by the International Collaborative Group (ICG) meeting in Amsterdam in 1990, and are known as the Amsterdam Criteria. However, these criteria are not considered comprehensive; a number of families who do not meet these criteria, but have germline MMR gene mutations, have been reported. For this reason, another set of clinical criteria that can be used to identify Lynch syndrome families is the revised Bethesda guidelines. These criteria are less stringent for identifying families with microsatellite instability (MSI) and germline mutations in one of the MMR genes (Mukherjee et al. 2010).

It is difficult to precisely determine the prevalence of HNPCC in children and adolescents with colorectal carcinoma. Case series reporting children and adolescents with colorectal cancer have not focused on the underlying genetic aspects of the tumor or genetic susceptibility of the families (Bethel et al. 1997; Vastyan et al. 2001; Kam et al. 2004). Single case reports describe adolescents with colorectal carcinoma with HNPCC, one 13-years old with an MSH2 mutation (Madlensky et al. 1997), another 13-year old with a PMS2 mutation (Hamilton et al. 1995) and a 14-year old with an MLH1 mutation (Huang et al. 2001).

Extremely rarely MMR genes mutations can occur in homozygosis. Generally, homozygous or compound heterozygous MMR gene mutation carriers develop hematologic malignancies, brain tumors, or both in their first decade of life (Durno and Gallinger 2006).

References

Albrecht S, Haber RM, Goodman JC, Duvic M (1992) Cowden syndrome and Lhermitte-Duclos disease. Cancer 70:869–876

Al-Sukhni W, Aronson M, Gallinger S (2008) Hereditary colorectal cancer syndromes: familial adenomatous polyposis and lynch syndrome. Surg Clin North Am 88:819–844

Attard TM, Young RJ (2006) Diagnosis and management of gastrointestinal polyps: pediatric considerations. Gastroenterol Nurs 29:16–22

Bethel CA, Bhattacharyya N, Hutchinson C, Ruymann F, Cooney DR (1997) Alimentary tract malignancies in children. J Pediatr Surg 32:1004–1008; discussion 1008–1009

Boardman LA (2002) Heritable colorectal cancer syndromes: recognition and preventive management. Gastroenterol Clin North Am 31:1107–1131

Bouguen G, Manfredi S, Blayau M, Dugast C, Buecher B, Bonneau D, Siproudhis L, David V, Bretagne JF (2007) Colorectal adenomatous polyposis associated with MYH mutations: genotype and phenotype characteristics. Dis Colon Rectum 50:1612–1617

Brosens LA, van Hattem WA, Jansen M, de Leng WW, Giardiello FM, Offerhaus GJ (2007) Gastrointestinal polyposis syndromes. Curr Mol Med 7:29–46

Calva D, Howe JR (2008) Hamartomatous polyposis syndromes. Surg Clin North Am 88:779–817

Carlson GJ, Nivatvongs S, Snover DC (1984) Colorectal polyps in Cowden's disease (multiple hamartoma syndrome). Am J Surg Pathol 8:763–770

Chow LM, Baker SJ (2006) PTEN function in normal and neoplastic growth. Cancer Lett 241:184–196

Chow E, Macrae F (2005) A review of juvenile polyposis syndrome. J Gastroenterol Hepatol 20:1634–1640

Coburn MC, Pricolo VE, DeLuca FG, Bland KI (1995) Malignant potential in intestinal juvenile polyposis syndromes. Ann Surg Oncol 2:386–391

David SS, O'Shea VL, Kundu S (2007) Base-excision repair of oxidative DNA damage. Nature 447:941–950

Desai DC, Neale KF, Talbot IC, Hodgson SV, Phillips RK (1995) Juvenile polyposis. Br J Surg 82:14–17

Durno CA, Gallinger S (2006) Genetic predisposition to colorectal cancer: new pieces in the pediatric puzzle (review). J Pediatr Gastroenterol Nutr 43:5–15

Eng C (2000) Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 37:828–830

Eng C, Ji H (1998) Molecular classification of the inherited hamartoma polyposis syndromes: clearing the muddied waters. Am J Hum Genet 62:1020–1022

Fackenthal JD, Marsh DJ, Richardson AL, Cummings SA, Eng C et al (2001) Male breast cancer in Cowden syndrome patients with germline PTEN mutations. J Med Genet 38:159–164

Forcet C, Billaud M (2007) Dialogue between LKB1 and AMPK: a hot topic at the cellular pole. Sci STKE 2007:pe51

Forcet C, Etienne-Manneville S, Gaude H, Fournier L, Debilly S et al (2005) Functional analysis of Peutz-Jeghers mutations reveals that the LKB1 C-terminal region exerts a crucial role in regulating both the AMPK pathway and the cell polarity. Hum Mol Genet 14:1283–1292

Giardiello FM, Trimbath JD (2006) Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol 4:408–415

Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM et al (1987) Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 316:1511–1514

Giardiello FM, Hamilton SR, Kern SE, Offerhaus GJ, Green PA et al (1991) Colorectal neoplasia in juvenile polyposis or juvenile polyps. Arch Dis Child 66:971–975

Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM et al (2000) Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 119:1447–1453

Gorlin RJ, Cohen MM Jr, Condon LM, Burke BA (1992) Bannayan-Riley-Ruval-caba syndrome. Am J Med Genet 44:307–314

Gryfe R (2009) Inherited colorectal cancer syndromes. Clin Colon Rectal Surg 22:198–208

Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, Krush AJ, Berk T, Cohen Z, Tetu B et al (1995) The molecular basis of Turcot's syndrome. N Engl J Med 332:839–847

Hemminki A, Tomlinson I, Markie D, Järvinen H, Sistonen P et al (1997) Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis. Nat Genet 15:87–90

Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S et al (1998) A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 391:184–187

Horrilleno EG, Eckert C, Ackerman LV (1957) Polyps of the rectum and colon in children. Cancer 10:1210–1220

Huang SC, Lavine JE, Boland PS, Newbury RO, Kolodner R, Pham TT, Arnold CN, Boland CR, Carethers JM (2001) Germline characterization of early-aged onset of hereditary non-polyposis colorectal cancer. J Pediatr 138:629–635

Jass JR, Williams CB, Bussey HJ, Morson BC (1988) Juvenile polyposis – a precancerous condition. Histopathology 13:619–630

Jenkins MA, Croitoru ME, Monga N, Cleary SP, Cotterchio M, Hopper JL, Gallinger S (2006) Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev 15:312–314

Jenne DE, Reimann H, Nezu J, Friedel W, Loff S et al (1998) Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet 18:38–43

Kam MH, Eu KW, Barben CP, Seow-Choen F (2004) Colorectal cancer in the young: a 12-year review of patients 30 years or less. Colorectal Dis 6:191–194

Kundu JK, Choi KY, Surh YJ (2006) beta-Catenin-mediated signaling: a novel molecular target for chemoprevention with anti-inflammatory substances. Biochim Biophys Acta 1765: 14–24

Kutscher AH, Zegarelli EV, Rankow RM, Slaughter TW (1960) Incidence of Peutz-Jeghers syndrome. Am J Dig Dis 5:576–577

Longy M, Coulon V, Duboue B, David A, Larrègue M et al (1998) Mutations of PTEN in patients with Bannayan-Riley-Ruvalcaba phenotype. J Med Genet 35:886–889

Madlensky L, Bapat B, Redston M, Pearl R, Gallinger S, Cohen Z (1997) Using genetic information to make surgical decisions: report of a case of a 13-year-old boy with colon cancer. Dis Colon Rectum 40:240–243

Manfredi M (2010) Hereditary hamartomatous polyposis syndromes. Gastroenterol Hepatol 6:185–196

Marignani PA (2005) LKB1, the multitasking tumour suppressor kinase. J Clin Pathol 58:15–19

Marsh DJ, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ et al (1999) PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet 8:1461–1472

McGarrity TJ, Wagner Baker MJ, Ruggiero FM, Thiboutot DM, Hampel H et al (2003) GI polyposis and glycogenic acanthosis of the esophagus associated with PTEN mutation positive Cowden syndrome in the absence of cutaneous manifestations. Am J Gastroenterol 98:1429–1434

Mehenni H, Blouin JL, Radhakrishna U, Bhardwaj SS, Bhardwaj K et al (1997) Peutz-Jeghers syndrome: confirmation of linkage to chromosome 19p13.3 and identification of a potential second locus, on 19q13.4. Am J Hum Genet 61:1327–1334

Miyoshi H, Nakau M, Ishikawa TO, Seldin MF, Oshima M, Taketo MM (2002) Gastrointestinal hamartomatous polyposis in Lkb1 heterozygous knockout mice. Cancer Res 62:2261–2266

Mukherjee A, McGarrity TJ, Ruggiero F, Koltun W, McKenna K, Poritz L, Baker MJ (2010) The revised Bethesda guidelines: extent of utilization in a university hospital medical center with a cancer genetics program. Hered Cancer Clin Pract 8:9

Nelen MR, van Staveren WC, Peeters EA, Hassel MB, Gorlin RJ et al (1997) Germline mutations in the PTEN/MMAC1 gene in patients with Cowden disease. Hum Mol Genet 6:1383–1387

Saab R, Furman WL (2008) Epidemiology and management options for colorectal cancer in children. Paediatr Drugs 10:177–192

Signoroni S, Vitellaro M, Sala P, Bertario L (2010) Biomarkers in familial adenomatous polyposis: role and significance (review). Front Biosci (Schol Ed) 2:413–421

Starink TM, van der Veen JP, Arwert F, de Waal LP, de Lange GG et al (1986) The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet 29:222–233

Suzuki A, de la Pompa JL, Stambolic V, Elia AJ, Sasaki T et al (1998) High cancer susceptibility and embryonic lethality associated with mutation of the PTEN tumor suppressor gene in mice. Curr Biol 8:1169–1178

Traboulsi EI, Maumenee IH (1986) Periocular pigmentation in the Peutz-Jeghers syndrome. Am J Ophthalmol 102:126–127

Utsunomiya J, Gocho H, Miyanaga T, Hamaguchi E, Kashimure A (1975) Peutz-Jeghers syndrome: its natural course and management. Johns Hopkins Med J 136:71–82

Vasen HF, Möslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bülow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Järvinen H, Mecklin JP, Møller P, Myrhøi T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen J (2008) Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 57:704–713

Vastyan AM, Walker J, Pintér AB, Gerrard M, Kajtar P (2001) Colorectal carcinoma in children and adolescents – a report of seven cases. Eur J Pediatr Surg 11:338–341

Volikos E, Robinson J, Aittomäki K, Mecklin JP, Järvinen H et al (2006) LKB1 exonic and whole gene deletions are a common cause of Peutz-Jeghers syndrome. J Med Genet 43:e18

Waite KA, Eng C (2002) Protean PTEN: form and function. Am J Hum Genet 70:829–844

Westerman AM, Wilson JH (1999) Peutz-Jeghers syndrome: risks of a hereditary condition. Scand J Gastroenterol 230:64–70

Zbuk KM, Eng C (2007) Hamartomatous polyposis syndromes. Nat Clin Pract Gastroenterol Hepatol 4:492–502

Tumors of the Esophagus and the Stomach

31

Dietrich von Schweinitz

Contents

31.1 Tumors of the Esophagus

In contrast to adults, neoplastic tumors of the esophagus are exceedingly rare during childhood and adolescence (Pappo and Furman 2006). As primary tumors of other parts of the gastrointestinal tract, also those of the esophagus almost never affect infants and toddlers but rather school-age children and adolescents (Ladd and Grosfeld 2006). In the SEER registry of 1992–2007, a rate of < .02 per 1 million children was documented. But also in this age group, carcinomas are the most frequent neoplasms and both adenocarcinomas and squamous cell carcinomas can occur (Pappo and Furman 2006). Esophageal carcinomas may be more frequent in Asia than in Europe or North America proposedly both on the basis of environmental and on genetic factors (Khushed et al. 2007). Adenocarcinomas of the esophagus in adults are usually associated with Barret's esophagus because of chronic gastroesophageal reflux, and there have been reports on this association also in children. Esophageal carcinomas can occur during childhood in the context of cancer predisposing syndromes and are more frequent in boys than in girls. According to reports on single patients, other malignant neoplasms as leiomyosarcomas and undifferentiated mesenchymal tumors and also benign tumors as leiomyomas, hamartomas, lipomas and fibromatosis can be found in children (Heij 2008).

Patients with an esophageal tumor usually present with dysphagia and weight loss. Other typical symptoms are vomiting, cough, regurgitation and hematemesis and retrosternal pain. In patients with these symptoms, other more-frequent causes as foreign body impactation, inflammatory diseases of the esophagus and malformations as bronchogenic cysts and esophageal duplications have to be ruled out. The

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SEER data 1992–2007															
Males and females				00–14 years		00–19 years		00–04 years		05–09 years		10–14 years		15–19 years	
ICCC code	ICCC	SRCode	Site recode	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
42	IX(d.1) Ewing tumor and Askin tumor of soft tissue	10	Esophagus	0	0	0.01	1	0	0	0	0	0	0	0.02	1
89	XI(f.10) Carcinomas of other specified sites	10	Esophagus	0.02	3	0.02	4	0	0	0.02	1	0.04	2	0.02	1
			Sum	**0.02**	**3**	**0.03**	**5**	**0**	**0**	**0.02**	**1**	**0.04**	**2**	**0.04**	**2**
38	IX(b.1) Fibroblastic and myofibroblastic tumors	11	Stomach	0.01	1	0.01	1	0	0	0	0	0.02	1	0	0
39	IX(b.2) Nerve sheath tumors	11	Stomach	0	0	0.01	1	0	0	0	0	0	0	0.02	1
47	IX(d.6) Leiomyosarcomas	11	Stomach	0.02	3	0.03	5	0	0	0.07	3	0	0	0.05	2
53	IX(e) Unspecified soft tissue sarcomas	11	Stomach	0.01	1	0.01	1	0	0	0	0	0.02	1	0	0
61	X(b.2) Malignant teratomas: extracranial/ extragonadal	11	Stomach	0.01	1	0.01	1	0.02	1	0	0	0	0	0	0
89	XI(f.10) Carcinomas of other specified sites	11	Stomach	0.01	2	0.1	19	0	0	0	0	0.04	2	0.4	17
91	XII(a.1) Gastrointestinal stromal tumor	11	Stomach	0.02	3	0.03	5	0	0	0.02	1	0.04	2	0.05	2
97	XII(b) Other unspecified malignant tumors	11	Stomach	0.01	1	0.01	2	0.02	1	0	0	0	0	0.02	1
			Sum	**0.09**	**12**	**0.21**	**35**	**0.04**	**2**	**0.09**	**4**	**0.12**	**6**	**0.54**	**23**

Table 31.1 TNM clinical classification of esophageal cancer

T – Primary tumor		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Carcinoma in situ/high-grade dysplasia	
T1	Tumor invades lamina propria, muscularis mucosae or submucosa	
	T1a	Tumor invades lamina propria or muscularis mucosae
	T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria	
T3	Tumor invades adventitia	
T4	Tumor invades adjacent structures	
	T4a	Tumor invades pleura, pericardium or diaphragm
	T4b	Tumor invades other adjacent structures such as aorta, vertebral body or trachea
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in 1–2 regional lymph nodes	
N2	Metastasis in 3–6 regional lymph nodes	
N3	Metastasis in 7 or more regional lymph nodes	
M – Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

diagnostic procedure should include conventional radiology with contrast medium, a CT or MRI scan and an esophagoscopy with biopsies. Early stage tumors are asymptomatic and may be found incidentally during endoscopy for other reasons. A histological confirmation of the diagnosis is mandatory. In case of malignancy, other diagnostic procedures as thoracic CT, bone scan, FDG-PET scan and cerebral MRI become necessary for identification of metastases and staging. Esophageal carcinomas are staged according to the TNM system (Table 31.1; Sobin et al. 2009).

The mainstay of treatment of esophageal tumors is a complete surgical resection. Depending on tumor extension, this can be accomplished by a local excision or by a removal of the esophagus with a replacement by either a gastric or a colonic interposition. In case of a malignant tumor, especially a carcinoma, it is important to perform a thorough lymph node dissection. Adjuvant chemotherapy and/or radiation may be administered for malignant neoplasms. In carcinomas these are of very little to no effect, while in sarcomas they can be cytotoxic in a regime according to the existing different national and international soft tissue sarcoma trials (Pappo and Furman 2006).

The prognosis of children with a benign tumor is good; however, depending of the extension of the tumor, long-term functional problems may be a result of surgical treatment. In case of mesenchymal neoplasms, the patients' chance for survival will be similar to that of the same entities (i.e. leiomyosarcoma, undifferentiated mesenchymal tumor) at other locations and the tumor extension. Other factors for survival are possible radicality of surgery and response of the tumor to chemotherapy and radiation. The prognosis of children with esophagus carcinoma has been dismal in the very few reported cases. This may be due to an advanced stage of disease at diagnosis, but possibly also of an increased aggressiveness of carcinomas in young patients in comparison to adults (Heij 2008).

31.2 Tumors of the Stomach

Although not as exceedingly rare in childhood and adolescence as esophageal neoplasms, primary tumors of the stomach occur only sporadically in the pediatric age group; thus only 0.05% of all gastric cancers are

found in children (Pappo and Furman 2006), and the SEER registry for 1992–2007 documented a rate of.21 per 1 million population <20 years of age. In contrast to adults, carcinomas do not comprise the vast majority of all gastric neoplasms of the young age. As primary benign tumors of the stomach, teratomas, hamartomas, lipomas, inflammatory myoblastic tumors, as well as leiomyomas and leiomyomatosis, have been described in children. Soft tissue sarcomas, mostly leiomyosarcomas, and lymphomas are the most common malignant tumors of the stomach in children; also GastroIntestinal Stroma Tumors (GIST) are found (Heij 2008; Curtis et al. 2008). Adenocarcinomas comprise only 5% of all gastric tumors in this age group (Pappo and Furman 2006). While as in adults the carcinomas seem to be associated with *Helicobacter pylori* infection, this was also proposed for lymphomas in childhood (Imrie et al. 2001). Gastric neoplasms may also be associated with tumor predisposing syndromes in children. A combination of GIST with extra-adrenal paraganglioma and pulmonary chondroma in children has been called Carney's triad.

Over 100 cases of gastric teratomas have been described in the literature (Heij 2008). These usually occur in early childhood and behave like teratomas of other localizations. Thus they usually are benign but with increasing age become malignant. Therefore, a complete excision is important at an early stage. Inflammatory myoblastic tumors occur rarely in the gastrointestinal tract. Here they are found mostly in the stomach. They are benign, grow slowly and do not metastasize, but often demonstrate local infiltration and a relatively high rate of local recurrences after surgery. Leiomyomas can grow in the stomach mainly in young children. As they are essentially benign tumors, surgical resection usually leads to cure.

Also malignant leiomyosarcomas are mostly found in children of young age; a number of these occur during the newborn period (Ladd and Grosfeld 2006). Other cases have been described in patients with a depression of the immune system, e.g. after organ transplantation or HIV infection. These tumors are highly malignant with a frequent development of metastases (Heij 2008). Some lymphomas are thought to develop from atopically arising mucosa associated lymphatic tissue (MALT) after a *Helicobacter pylori* infection, which then can develop into a low malignant lymphoma. These MALT lymphomas are usually locally spreading and seldomly disseminate. In a longer course of disease however, they can transform into highly malignant lymphomas, which takes place in 20% of the cases (Imrie et al. 2001). However, also typical Burkitt lymphomas of the stomach have been found in some pediatric cases.

GIST is a malignant mesenchymal tumor arising from primitive precursor cells which are related to the interstitial cells of Cajal. The majority (88%) of GISTs occurring in children are located in the stomach and are diagnosed in school-age girls (Miettinen et al. 2005). The biological and histological characteristics of GISTs are described in detail in a separate chapter of this book. Some GISTs of the stomach metastasize at local lymph nodes and the liver. The response rate of GISTs in children to imatinib mesylate is estimated to be approximately 50%.

The very rare carcinomas of the stomach in school-age children and adolescents do not seem to differ very much from those in adults concerning histopathology and biological behavior. Thus, they grow locally aggressive and spread via lymphatic and blood vessels as well as by peritoneal seeding. Therefore, they can involve adjacent organs such as esophagus, duodenum, pancreas, colon and liver. Distant metastases can affect the liver, lungs, bones and skin (Pappo and Furman 2006). The tumor status and the extension of disease can best be classified with the TNM system (Table 31.2; Sobin et al. 2009).

The clinical symptoms of gastric tumors are quite uniform. The patients have epigastric discomfort or pain, nausea and vomiting, sometimes anorexia and weight loss. Also hematemesis and anemia as well as occult blood in the stool may appear. Often the tumor is palpable in the upper abdomen at the time of diagnosis. For differential diagnosis, mainly space-occupying malformations of the stomach, especially a gastric duplication, have to be taken into account, but also extragastric tumors such as tumors of the pancreas, the liver and the retroperitoneum. Therefore besides a laboratory work-up, the diagnostic procedures should include abdominal ultrasound, radiology with an upper gastrointestinal contrast medium passage, a CT and/or MRI scan and a gastroscopy. During this procedure the essential biopsies can be taken. In case of malignancy, investigations for staging with thoracic CT, bone scan and eventually a FDG-PET scan should follow. In patients with a suspected gastric lymphoma, it is important to gain tumor material through a biopsy or

Table 31.2 TNM clinical classification of gastric cancer

T – Primary tumor		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia	
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa	
	T1a	Tumor invades lamina propria or muscularis mucosae
	T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria	
T3	Tumor invades subserosa	
T4	Tumor perforates serosa or invades adjacent structures[a–c]	
	T4a	Tumor perforates serosa
	T4b	Tumor invades other adjacent structures[a–c]
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in 1–2 regional lymph nodes	
N2	Metastasis in 3–6 regional lymph nodes	
N3	Metastasis in 7 or more regional lymph nodes	
	N3a	Metastasis in 7–15 regional lymph nodes
	N3b	Metastasis in 16 or more regional lymph nodes
M – Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

[a]The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum

[b]Intramural extension of the duodenum or esophagus is classified by the depth of greatest invasion in any of these sites, including stomach

[c]Tumor that extends into gastrocolic or gastrohepatic ligaments or into greater or lesser omentum, without perforation of visceral peritoneum, is T3

from other material as ascites, pleural effusion or bone marrow before planning of treatment.

The best therapy for most gastric tumors is a primary complete resection (Heij 2008). Obviously this has to be more extensive in malignant than in benign tumors. Therefore if the diagnosis is not established by a biopsy beforehand, intraoperative frozen sections should be performed by the pathologist. In benign tumors a local excision usually with preservation of some parts of the stomach is sufficient. In contrast to malignant tumors, a resection with wide margins and excision of regional lymph nodes is the procedure of choice. For pediatric GIST and sarcomas but also for gastric carcinomas, it is not clear whether a limited lymph node dissection with a low rate of surgical complication or an extended dissection with a high risk of complications is the better procedure. In relatively extended tumors, complete gastrectomies can be performed also in children without taking a risk for acute complications and long-term sequelae which would be higher than in adults.

Only for gastric lymphomas as for non-Hodgkin's lymphomas of other sites, the treatment of choice is primary chemotherapy according to the schemes of non-Hodgkin's lymphoma trials. In most cases this is very effective and the tumors show an extensive decrease of size. In some patients in whom this diagnosis has been established before start of treatment, surgery is not necessary any more after a complete regression of the tumor (Pappo and Furman 2006).

Adjuvant therapy is indicated in many cases with another malignant tumor. In sarcomas, chemotherapy

according to the different soft tissue sarcoma protocols often has at least some effect, and in cases of GIST, adjuvant therapy should mainly contain imatinib mesylate. Although gastric carcinomas mostly show a very poor response to chemotherapy, different cytotoxic agents such as 5-FU, doxorubicin, cisplatin, etoposide, mitomycin and irinotecan have been administered adjuvantly. Sarcomas and some carcinomas are responsive to radiation which may preferably be administered in addition to chemotherapy, especially after marginal resections. Patients with unresectable or metastasized malignant tumors should receive neoadjuvant treatment. For sarcomas the chemotherapy regimens shown to be effective in soft tissue sarcomas of other localizations should be applied. For GIST, imatinib mesylate should be administered while the effect of conventional chemotherapy is not clear especially in children. In extended unresectable and/or metastasized carcinomas, pre- or intraoperative radiation but also chemotherapy can be tried (Pappo and Furman 2006).

The prognosis of gastric tumors depends on the dignity, the histological diagnosis, the extension of disease, surgical resectability and the response to chemotherapy and radiation. Benign tumors usually have a very good prognosis. This also accounts for gastric lymphomas, while the prognosis for sarcomas is dependent on resectability and sensitivity to chemotherapy and radiation. For GIST it seems that children have a slightly poorer outcome than adults; approximately two thirds of the pediatric patients could be cured in the recent years (Cypriano et al. 2004). The prognosis of gastric carcinoma in childhood is very poor; only very few survivors have been reported (Pappo and Furman 2006; Heij 2008).

References

Curtis JL, Burns RC, Wang L et al (2008) Primary gastric tumors of infancy and childhood: 54-year experience at a single institution. J Pediatr Surg 43:1487–1493

Cypriano MS, Jenkins JJ, Pappo AS et al (2004) Pediatric gastrointestinal stromal tumors and leiomyosarcoma. Cancer 101:29–50

Heij HA (2008) Rare tumors. In: Carachi R, Grosfeld JL, Azy AF (eds) The surgery of childhood tumors, 2nd edn. Springer, Heidelberg

Imrie C, Rowland M, Bourke B et al (2001) Is *Helicobacter pylori* infection in childhood a risk factor for gastric cancer? Pediatrics 107:373–380

Khushed A, Ahmed R, Bhurgri Y (2007) Primary gastrointestinal malignancies in childhood and adolescents – an Asian perspective. Asian Pac J Cancer Prev 8:613–617

Ladd AP, Grosfeld JL (2006) Gastrointestinal tumors in children and adolescents. Semin Pediatr Surg 15:37–47

Miettinen M, Lasota J, Sobin LH (2005) Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Pathol 29:1373–1381

Pappo AS, Furman WL (2006) Management if infrequent cancers of childhood. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology, 5th edn. Lippincott Williams & Wilkins, Philadelphia, pp 1173–1201

SEER Registry 1992–2007 www.seer.cancer.gov

Sobin LH, Gospodarowicz MK, Wittekind C (2009) TNM classification of malignant tumours (UICC International Union Against Cancer), 7th edn. Wiley, New York

Intestinal Carcinomas

32

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Contents

Carcinomas of the small intestine, colon, and rectum are malignant epithelial tumors, originating from glandular epithelium of the intestinal mucosa. They represent one of the leading malignancies among adults worldwide. While adenocarcinoma of the small bowel (duodenum, jejunum, and ileum) is less frequent, colorectal carcinoma (CRC) is the third most common malignancy in adults worldwide after lung and breast cancers, with 945,000 new cases a year (9.4% of the world total) and 492,000 deaths (7.9% of the total) (Parkin 2001). However, these tumors are extremely rare among children, particularly before puberty (Fig. 32.1). In the Survival Epidemiology and End Result (SEER) public-access database, only 31 cases younger than 15 years old and 143 aged from 15 to 19 years old were collected between 1973 and 2006, as compared to 584,427 adult cases (Ferrari et al. 2010). Age-adjusted incidence rates calculated from the SEER database in children/adolescents and adults were reported to be 0.38 and 802 per million, respectively (Sultan et al. 2010). Therefore, pediatric oncologists and pediatric surgeons only occasionally encounter these tumors in their clinical activity. When this happens, their limited experience and the scanty data available in the literature make the management of these patients a real challenge; also, because the clinical appearance, the anatomical sites involved, the tumor's clinical course, but also the related risk stratification, the applicable staging systems and recommended investigations, as well as the therapeutic procedures, are generally very different from what pediatric oncologists have learnt from years of experience in managing typical childhood embryonal tumors.

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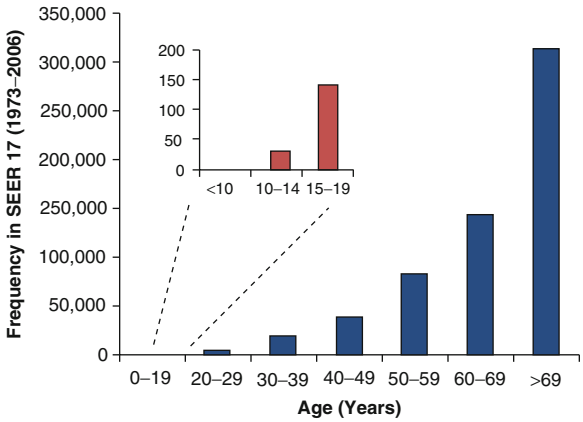

Fig. 32.1 Colorectal cancer by age from the Survival Epidemiology and End Result (SEER) public-access database (1973–2007) (www.seer.cancer.gov) (Courtesy by Dr. Iyad Sultan, King Hussein Cancer Center, Amman, Jordan)

32.1 Pediatric Series: Peculiarities of Disease When Arising in Children

Table 32.1 shows some of the major reports on CRC of children and adolescents, published in the last two decades. Various reports have been published on series of CRC in young people, but most of these studies included patients up to the age of 30 or more, treated over lengthy periods of time. As a matter of fact, the real number of prepubertal cases (or under-18-year-olds at least) is only a few dozen (Andersson and Bergdahl 1976; Bhatia et al. 1999; Brown et al. 1992; Chantada et al. 2005; Chen et al. 2001; Chung et al. 1998; Cozart et al. 1993; Durno et al. 2005; Ferrari et al. 2008; Hill et al. 2007; Kam et al. 2004; Karnak et al. 1999; Kravarusic et al. 2007; Lamego and Torloni 1989; LaQuaglia et al. 1992; Lee et al. 1994; Minardi et al. 1998; Pratt et al. 1999; Radhakrishnan and Bruce 2003; Rao et al. 1985; Rodriguez-Bigas et al. 1996; Salas-Valverde et al. 2009; Sebbag et al. 1997; Shahrudin and Noori 1997; Stones and McGill 2003; Sule and Mandong 1999; Taguchi et al. 1991; Vastyan et al. 2001). The largest hospital-based series included 77 children and adolescents (up to 19 years of age) referring to the St Jude Children's Research Hospital over a period of 40 years (Hill et al. 2007). Recently, a comprehensive literature review (Saab and Furman 2008) and a population-based study using the SEER data (Sultan et al. 2010) were published. The latter, in particular, compared the clinical features and outcomes of 159 patients less than 20 years old (only 12 cases were under 12 years old) with those of a large cohort of over 550,000 adult cases.

Despite of the limited sources, all the published experiences were consistent in drawing a similar picture, suggesting that CRC in children may behave differently when they occur in adults. Hallmarks of this tumor in the younger age groups are: (1) a higher incidence of unfavorable aggressive histotypes, (2) an advanced clinical stage at onset (in many cases with peritoneal carcinomatosis), and (3) a worse survival rate for pediatric cases than for adults.

As for the first of these features, all the publications report frequently finding poorly-differentiated or signet-ring or mucinous adenocarcinoma subtypes in children and adolescents. On the contrary, most tumors in adults are moderately or well differentiated. This may suggest that CRC in pediatric age is biologically more aggressive. The reasons for this situation remain substantially unclear. In addition to this high incidence of unfavorable histotypes, particular microsatellite instability has also been reported in younger patients (Kim et al. 2003). New studies are needed to clarify speculative hypotheses on the tumorigenesis of childhood CRC differing from the well-known multistep process occurring in adults (which is assumed to take around 10 years) and probably taking an alternative, shorter path (Durno et al. 2005; Fearon 1997). The rarity of the tumor in childhood and the fact that tissue collections are unavailable make biological studies on the disease's pathogenesis extremely difficult.

The second peculiarity of CRC in children is the advanced stage at onset: in the SEER review, only 19% of children/adolescents had localized disease, while their chances of having distant spread was twice as high as in adults (Sultan et al. 2010). Clearly, the possible different biological aggressiveness of CRC in pediatric age may have a relevant role in determining the initial spread of the disease. However, some studies suggested that diagnostic delays may have a role as well (Karnak et al. 1999; Lamego and Torloni 1989; Rao et al. 1985; Salas-Valverde et al. 2009): long symptom intervals have been reported on various occasions for children with CRC, e.g., in a recent Argentina series, the median time elapsing between the first symptoms and diagnosis was reportedly 3 months for patients less than 20 years old, as opposed to 1 month for those over 20 (Chantada et al. 2005). This finding may be related to the scarce awareness (not only of

Table 32.1 Major reports on colorectal carcinoma of children and adolescents, published in the last two decades

Author	Patients	Comments
La Quaglia MP, 1992 Memorial Sloan-Kettering Cancer Center, New York	29 pts < 21 years, in a 40-year period	3-years survival 28%, very high incidence of high-grade histologies
Cozart DT, 1993 Little Rock, Arkansas	55 pts < 30 years from 24 different centers	5-years survival 56% – feasibility of studies on rare tumors using a registry framework
Rodriguez-Bigas MA, 1996 Buffalo, NY	68 pts < 30 years (median age 27 year), in a 25-year period	Poor prognosis (only 9 pts were alive)
Chung YFA, 1998 Singapore General Hospital	23 pts < 29 years (out of 110 < 40 year)	Young age is not a clear poor prognostic marker
Karnak I, 1999 Ankara, Turkey	20 pts < 16 years	Delayed diagnosis, advanced disease, and mucinous type determine poor outcome
Pratt CB, 1999 St. Jude Children's Research Hospital, Memphis	13 pts 11–23 years of age	5-fluorouracil, leucovorin, α-interferon for advanced disease
Bhatia S, 1999 St. Jude Children's Research Hospital, Memphis	53 pts < 21 years seen from 1960 to 1998	25 cases: interview on family history on cancer, resulting in an increased risk of colorectal cancer in relatives
Sule AZ, 1999 Nigeria	35 cases < 30 years (median age 25 years)	Poor prognosis
Vastyan AM, 2000 Pecs, Hungary/Sheffield, UK	7 cases < 15 years	Poor outcome
Chen LK, 2001 Taiwan	28 cases < 20 years	No crucial role for family history, inflammatory bowel disease, or familial polyposis
Radhakrishnan CN, 2003 Manchestern, UK	8 pts < 16 years	All died of tumor
Durno C, 2005 Toronto, Canada	16 cases < 24 years	Genetic analysis: inherited predisposition for early-onset cases
Chantada GL, 2005 Buenos Aires, Argentina	14 pts < 20 years, compared to 7 from 21 to 30 years	Advanced disease and poor prognosis for pts < 20 years
Kravarusic D, 2007 Israel	7 children	Poor outcome, delayed diagnosis
Hill DA, 2007 St. Jude Children's Research Hospital, Memphis	77 children and adolescents (ages 7–19 years), from 1964 to 2003	High frequency of mucinous histology, Poor outcomes
Ferrari A, 2008 Istituto Nazionale Tumori, Milan, Italy	7 children (<18 years) compared to 20 young adults (<30 years) and 2,340 older adults	Rarity and poor prognosis (advanced stage, aggressive biology) Young adults similar to older adult series
Salas-Valverde S, 2009 San Josè, Costarica	11 children	A high level of awareness and early diagnosis are critical
Sultan I, 2010 Amman, Jordan SEER (Surveillance, Epidemiology and End Results) database	159 children/adolescents (ages 4–20 years) comparison with adults	High-risk features and worse outcome than adults

young people, but also of their parents and physicians) that CRC can occur in this age group. It is assumed that adolescents do not get cancer, and particularly not this type; so, little clinical attention is paid to telltale signs, and the rather vague and nonspecific symptoms (mild abdominal pain, constipation or diarrhea, hematochezia, weight loss) are often underestimated. Moreover, even when the disease is suspected, its diagnosis

by means of a fiberoptic exam may be more difficult in children, and rectosigmoidoscopy may fail to identify the tumor because of the relatively high frequency of right-sided lesions (while in most adult cases of colonic cancer, the tumor is usually located within 25 cm of the anus) (Ferrari et al. 2008).

Finally, pediatric CRC cases are characterized by a worse survival than adults. The study on the SEER series showed survival estimates at 5 and 10 years of 40% and 31% for children/adolescents and 60% and 54% for adults (Sultan et al. 2010); furthermore, no improvement in survival rates seemed to be between 1973 and 2005 for the children/adolescents included in the SEER database. The poor prognosis for pediatric CRC may be related to various factors. Above all, these tumors usually present in an advanced stage and with aggressive histological features. An advanced stage at diagnosis is a variable that affects survival not only in itself but also because it strongly reduces the chances of adequate surgery: CRC remains a primarily "surgical disease" and the rate of complete resection in children is reportedly suboptimal, to say the least (Rao et al. 1985). Whether the rarity of the tumor and the inexperience of pediatric oncologists and surgeons contribute to the poor outcome for children with CRC is hard to say, but it may be of interest to recall that some adult studies have identified the surgeon's experience and level of specialization as a prognostic variable (Simons et al. 1997; Porter et al. 1998).

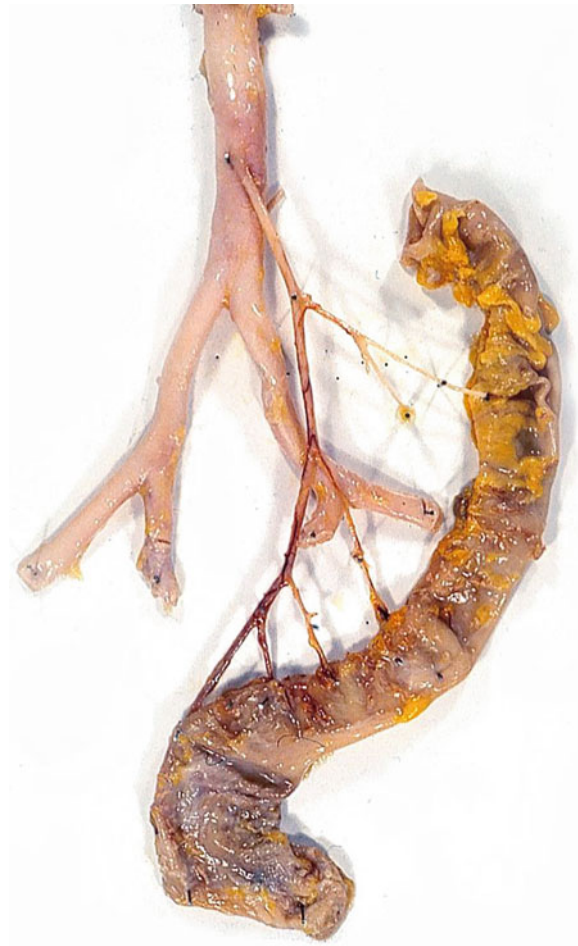

Fig. 32.2 From an autopsy: advanced rectal tumor (Courtesy by Dr. Gianfranco Gallino, Colorectal Cancer Surgery Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy)

32.2 Diagnosis

Initial signs and symptoms may be aspecific. Local symptoms include changes in bowel habit (new-onset constipation or diarrhea in the absence of another cause), rectal tenesmus, and reduction in diameter of stool, bleeding, or increased presence of mucus. In advanced cases, bowel obstruction may occur (Fig. 32.2). In case of chronic occult bleeding, iron-deficiency anemia with fatigue, palpitations, and pallor may be the initial sign. Weight loss is a frequent constitutional symptom (Table 32.2).

In case of suspected signs or symptoms, first-level investigations may be digital rectal exam, fecal occult blood test, abdominal ultrasound, and colonoscopy with eventual biopsy. Tumor stage is based on surgery and histopathological diagnosis. Computed tomography (CT) scan and positron emission tomography (PET) are required for the detection of metastases. The level of carcinoembryonic antigen (CEA) in the blood and, less significantly, CA19-9 and CA 242 are markers of the disease (especially for adenocarcinoma). CEA may be used to monitor and assess response to treatment in patients with metastatic disease and can also be used to monitor recurrence.

The most common staging system is the TNM (for tumors/nodes/metastases) system, from the American Joint Committee on Cancer (AJCC 2002) (Table 32.2), based on the level of the invasion of the primary tumor (mucosa, submucosa, muscularis propria, sierosa, or beyond) and the number of lymph node metastases (Fig. 32.3). Other previously used staging classifications are the Dukes and the Astler-Coller classifications.

Table 32.2 A general view: practical diagnostic and therapeutic guidelines for colorectal carcinoma of children and adolescents

Physical examination	Signs and symptoms (constipation/diarrhea, tenesmus, bleeding, bowel obstruction, fatigue, palpitations, pallor, weight loss)
	Anamnesis: familiarity (genetic counseling)
Laboratory assessment	Fecal occult blood test, iron-deficiency anemia
	Carcinoembryonic antigen (CEA) blood level
	Genetic testing
Radiological assessment	
– First assessment	Digital rectal exam, abdominal ultrasound and colonoscopy
– Local staging	Abdominal Computed Tomography (CT) scan
	Surgical staging
– Diagnostic work	Chest and abdominal CT scan, positron emission tomography (PET)
Pathological assessment	Usually follows tumor resection
	Reports on tumor subtype and grade (well, moderately, and poorly differentiated)
	Defines local staging
Staging systems for risk-adapted treatment strategy	*TNM AJCC system*
	Stage 0 – Tis N0 M0 – Tis: Tumor confined to mucosa, cancer in situ
	Stage I – T1 N0 M0 – T1: Tumor invades submucosa
	Stage I – T2 N0 M0 – T2: Tumor invades muscularis propria
	Stage II-A – T3 N0 M0 – T3: Tumor invades subserosa or beyond (without other organs involved)
	Stage II-B – T4 N0 M0 – T4: Tumor invades adjacent organs or perforates the visceral peritoneum
	Stage III-A – T1-2 N1 M0 – N1: Metastasis to 1 to 3 regional lymph nodes. T1 or T2
	Stage III-B – T3-4 N1 M0 – N1: Metastasis to 1 to 3 regional lymph nodes. T3 or T4
	Stage III-C – any T, N2 M0 – N2: Metastasis to 4 or more regional lymph nodes. Any T
	Stage IV – any T, any N, M1 – M1: Distant metastases present. Any T, any N
General treatment guidelines	Need for multidisciplinary approach
	Need for referral to prime oncology center with expert physicians professionally dedicated to the management of this cancer in adults (or strict collaboration with them)
– Surgery	Keystone of treatment
	Consider multivisceral resections, peritonectomy, or procedures as hyperthermic intraperitoneal chemoperfusion (HIPEC)
– Radiotherapy	Defined role for rectal cancer
– Chemotherapy	Adjuvant chemotherapy for stage III
	FOLFOX – 5-fluorouracil, leucovorin, oxaliplatin
	FOLFIRI –5-fluorouracil, leucovorin, and irinotecan
	Chemotherapy with novel agents for advanced disease

32.3 Treatment

Since the rarity of the tumor prevents the feasibility of clinical trials dedicated to pediatric CRC, the therapeutic recommendations should stay the same as for adults, i.e., a multimodality treatment guided by precise staging and histopathology. Surgery is unquestionably the keystone of the treatment for localized cases, and must be timely, adequate, and radical, taking into consideration even wide or multivisceral resections as well as peritonectomy or procedures as hyperthermic intraperitoneal chemoperfusion (HIPEC). Very early cancer that develops within a polyp can often be cured by polypectomy at colonoscopy. More advanced cases require the resection of the section of colon containing the tumor with sufficient margins, en bloc with mesentery, and lymph nodes (radical colectomy). Laparoscopic-assisted colectomy may be used in some cases to reduce surgical morbidity. Since surgery remains the most reliable way to cure patients with CRC, early diagnosis is crucial: it is important for pediatricians to be aware that CRC does occur in children so that they can refer suspect cases to a prime oncology center with expert physicians professionally dedicated to the management of this cancer in adults. Close cooperation with adult surgeons and medical

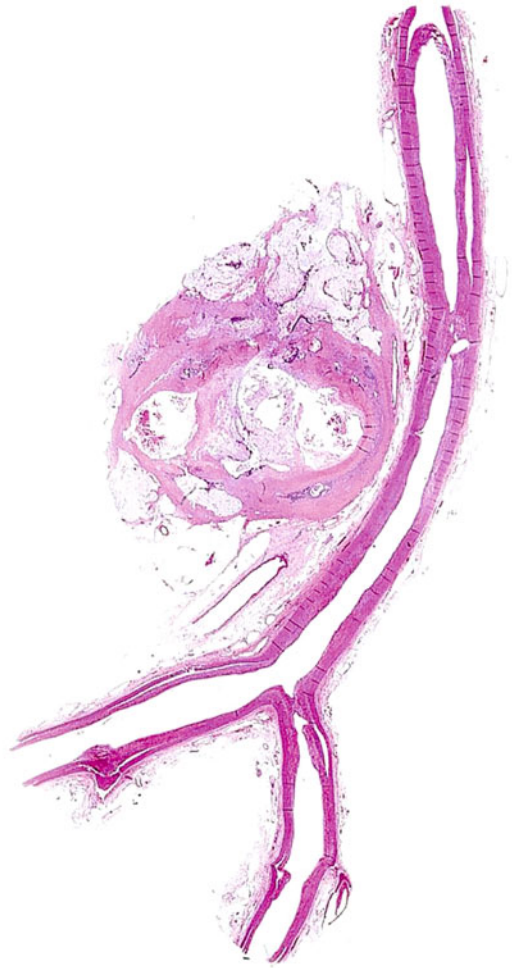

Fig. 32.3 Lymph node metastasis of colorectal carcinoma adjacent to vessel (Courtesy by Dr. Gianfranco Gallino, Colorectal Cancer Surgery Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy)

oncologists is crucial to improve quality of cure for children and adolescents with CRC.

The indication for adjuvant treatment depends on the individual patient's staging and, again, should follow the recommendations in the guidelines for adult CRC. Survival for early stage tumors (TNM stage T1-2, N0, M0) is over 90% at 5 years: in this case, surgery may be the only treatment.

For patients with resected CRC with lymph nodes involvement (stage III), adjuvant chemotherapy based on 5-fluorouracil/folinic acid (5-FU/FA) is a standard practice (Madajewicz et al. 1984; Minsky et al. 1995). More controversy exists concerning the optimal regimen and whether to treat node-negative patients at T3-4 stage. Various agents (i.e., capecitabine, oxaliplatin, irinotecan) have proved to be active in advanced disease and are now under evaluation in the adjuvant setting (Rothenberg et al. 2003; Goyle and Maraveyas 2005; Saltz et al. 2000). Novel targeted agents (i.e., bevacizumab, cetuximab, panitumumab, bortezomib, gefitinib) are considered of potential interest.

Postoperative radiotherapy has a definite role for rectal cancer (particularly combined with 5-FU-based chemotherapy), although more emphasis has recently been placed on preoperative radiotherapy for advanced cases, to decrease the risk of recurrence following surgery or to allow for less invasive surgical approaches (such as a low anterior resection instead of an abdominoperineal resection) (Minsky et al. 1992, 1997). Its use in colon cancer is limited by the difficulties to target the tumor volume and the risk of radiation enteritis. The treatment of liver metastases includes surgical resection, but also alternative modalities as radio-frequency ablation, cryoablation, and chemoembolization.

32.4 Risk Factors

Most of the risk factors related to lifestyle that have been described for adult CRC (smoking, diet high in red meat and low in fresh fruit and vegetables, alcohol, physical inactivity) are most unlikely to play a role in the pathogenesis of CRC in children. If prevention based on improving lifestyle is not feasible in children, focus should be directed to early diagnosis and increased surveillance in the case of familiarity.

Bowel cancer has been defined as the most frequent form of hereditary neoplasia (Fearon 1997), and approximately 10–20% of CRC occur in familial aggregations, in particular in familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Genetic counseling is mandatory for young people with CRC. However, the association of these inherited autosomal dominant conditions with early-onset tumors seem to be more common in young adults than in children (Durno et al. 2005; Ferrari et al. 2008; Losi et al. 2005; Leppert et al. 1987; Pinto et al. 2006), and it is still debated whether a family history of bowel cancer increases the risk of CRC in pediatric age, i.e., the tumorigenesis of childhood CRC may differ from the well-described multistep process of adult CRC (which usually takes around 10 years).

References

AJCC (2002) AJCC cancer staging manual, vol 6. Springer, New York

Andersson A, Bergdahl L (1976) Carcinoma of the colon in children: a report of six new cases and a review of the literature. J Pediatr Surg 11:967–971

Bhatia S, Pratt CB, Sharp GB, Robison LL (1999) Family history of cancer in children and young adults with colorectal cancer. Med Pediatr Oncol 33:470–475

Brown RA, Rode H, Millar AJ et al (1992) Colorectal carcinoma in children. J Pediatr Surg 27:919–921

Chantada GL, Perelli VB, Lombardi MG et al (2005) Colorectal carcinoma in children, adolescents, and young adults. J Pediatr Hematol Oncol 27:39–41

Chen LK, Hwang SJ, Li AF et al (2001) Colorectal cancer in patients 20 years old or less in Taiwan. South Med J 94:1202–1205

Chung YF, Eu KW, Machin D et al (1998) Young age is not a poor prognostic marker in colorectal cancer. Br J Surg 85:1255–1259

Cozart DT, Lang NP, Hauer-Jensen M (1993) Colorectal cancer in patients under 30 years of age. Contributors to the Southwestern Surgical Congress Unusual Case Registry. Am J Surg 166:764–767

Durno C, Aronson M, Bapat B et al (2005) Family history and molecular features of children, adolescents, and young adults with colorectal carcinoma. Gut 54:1146–1150

Fearon ER (1997) Human cancer syndromes: clues to the origin and nature of cancer. Science 278:1043–1050

Ferrari A, Rognone A, Casanova M et al (2008) Colorectal carcinoma in children and adolescents: the experience of the Istituto Nazionale Tumori of Milan, Italy. Pediatr Blood Cancer 50:588–593

Ferrari A, Casanova M, Massimino M, Sultan I (2010) Peculiar features and tailored management of adult cancers occurring in pediatric age. Expert Rev Anticancer Ther 10:1837–1851

Goyle S, Maraveyas A (2005) Chemotherapy for colorectal cancer. Dig Surg 22:401–414

Hill DA, Furman WL, Billups CA et al (2007) Colorectal carcinoma in childhood and adolescence: a clinicopathologic review. J Clin Oncol 25:5808–5814

Kam MH, Eu KW, Barben CP et al (2004) Colorectal cancer in the young: a 12 year review of patients 30 years or less. Colorectal Dis 6:191–194

Karnak I, Ciftci AO, Senocak ME et al (1999) Colorectal carcinoma in children. J Pediatr Surg 34:1499–1504

Kim HC, Kim CN, Yu CS et al (2003) Methylation of the hMLH1 and hMSH2 promoter in early-onset sporadic colorectal carcinomas with microsatellite instability. Int J Colorectal Dis 18:196–202

Kravarusic D, Feigin E, Dlugy E et al (2007) Colorectal carcinoma in childhood: a retrospective multicenter study. J Pediatr Gastroenterol Nutr 44:209–211

Lamego CM, Torloni H (1989) Colorectal adenocarcinoma in childhood and adolescence. Report of 11 cases and review of the literature. Pediatr Radiol 19:504–508

LaQuaglia MP, Heller G, Filippa DA et al (1992) Prognostic factors and outcome in patients 21 years and under with colorectal carcinoma. J Pediatr Surg 27:1085–1089

Lee PY, Fletcher WS, Sullivan ES et al (1994) Colorectal cancer in young patients: characteristics and outcome. Am Surg 60:607–612

Leppert M, Dobbs M, Scambler P et al (1987) The gene for familial polyposis coli maps to the long arm of chromosome 5. Science 238:1411–1413

Losi L, Di Gregorio C, Pedroni M et al (2005) Molecular genetic alterations and clinical features in early-onset colorectal carcinomas and their role for the recognition of hereditary cancer syndromes. Am J Gastroenterol 100:2280–2287

Madajewicz S, Petrelli N, Rustum YM et al (1984) Phase I-II trial of high-dose calcium leucovorin and 5-fluorouracil in advanced colorectal cancer. Cancer Res 44:4667–4669

Minardi AJ Jr, Sittig KM, Zibari GB et al (1998) Colorectal cancer in the young patients. Am Surg 64:849–853

Minsky BD, Cohen AM, Kemeny N et al (1992) Enhancement of radiation-induced downstaging of rectal cancer by fluorouracil and high-dose leucovorin chemotherapy. J Clin Oncol 10:79–84

Minsky BD, Cohen AM, Enker WE et al (1995) Efficacy of postoperative 5-FU, high-dose leucovorin, and sequential radiation therapy for clinically resectable rectal cancer. Cancer Invest 13:1–7

Minsky BD, Cohen AM, Enker WE et al (1997) Preoperative 5-FU, low-dose leucovorin, and radiation therapy for locally advanced and unresectable rectal cancer. Int J Radiat Oncol Biol Phys 37:289–295

Parkin DM (2001) Global cancer statistics in the year 2000. Lancet Oncol 2:533–543

Pinto C, Veiga I, Pinheiro M et al (2006) MSH6 germline mutations in early-onset colorectal cancer patients without family history of the disease. Br J Cancer 95:752–756

Porter GA, Soskolne CL, Yakimets WW, Newman SC (1998) Surgeon-related factors and outcome in rectal cancer. Ann Surg 227:157–167

Pratt CB, Rao BN, Merchant TE et al (1999) Treatment of colorectal carcinoma in adolescents and young adults with surgery, 5-fluorouracil/leucovorin/interferon-alpha 2a and radiation therapy. Med Pediatr Oncol 32:459–460

Radhakrishnan CN, Bruce J (2003) Colorectal cancers in children without any predisposing factors. A report of eight cases and review of the literature. Eur J Pediatr Surg 13:66–68

Rao BN, Pratt CB, Fleming ID et al (1985) Colon carcinoma in children and adolescents. A review of 30 cases. Cancer 55:1322–1326

Rodriguez-Bigas MA, Mahoney MC, Weber TK et al (1996) Colorectal cancer in patients aged 30 years or younger. Surg Oncol 5:189–194

Rothenberg ML, Oza AM, Bigelow RH et al (2003) Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 21:2059–2069

Saab R, Furman WL (2008) Epidemiology and management options for colorectal cancer in children. Pediatr Drugs 10:177–192

Salas-Valverde S, Lizano A, Gamboa Y et al (2009) Colon carcinoma in children and adolescents: prognostic factors and outcome – a review of 11 cases. Pediatr Surg Int 25:1073–1076

Saltz LB, Cox JV, Blanke C et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343:905–914

Sebbag G, Lantsberg L, Arish A et al (1997) Colon carcinoma in the adolescent. Pediatr Surg Int 12:446–448

Shahrudin MD, Noori SM (1997) Cancer of the colon and rectum in the first three decades of life. Hepatogastroenterology 44:441–444

Simons AJ, Ker R, Groshen S et al (1997) Variations in treatment of rectal cancer: the influence of hospital type and caseload. Dis Colon Rectum 40:641–646

Stones DK, McGill N (2003) Colon carcinoma in African children. Med Pediatr Oncol 40:410–411

Sule AZ, Mandong BM (1999) Malignant colorectal tumours in patients 30 years and below: a review of 35 cases. Cent Afr J Med 45:209–212

Sultan I, Rodriguez-Galindo C, El-Tani H et al (2010) Colorectal cancer in children and adolescents: a population based study of 159 cases with comparison to adult cases. Cancer 116:758–765

Taguchi T, Suita S, Hirata Y et al (1991) Carcinoma of the colon in children: a case report and review of 41 Japanese cases. J Pediatr Gastroenterol Nutr 12:394–399

Vastyan AM, Walker J, Pinter AB et al (2001) Colorectal carcinoma in children and adolescents – a report of seven cases. Eur J Pediatr Surg 11:338–341

Neuroendocrine Tumors of the Appendix

33

Antje Redlich, Nicole Boxberger, and Peter Vorwerk

Content

Neuroendocrine tumors (NET) of the appendix have a more favorable prognosis than other NET in the gastrointestinal system and should therefore be considered separately. The term "carcinoid" was introduced in the beginning of the last century to indicate the more benign behavior of this type of tumor compared to adenocarcinoma and is still widely used (Oberndorfer 1907; Stinner and Rothmund 2005). The good prognosis of the appendical NET seems to be a consequence of a different neuroendocrine origin of the tumor cells in the appendix (Lundqvist and Wilander 1987; Shaw 1991) and also of the clinical symptoms and early removal of the whole organ. Moreover, NET of the appendix usually do not metastasize when the tumor is smaller than 1 cm (Prommegger et al. 2002; Redlich et al. 2009).

Most NET of the appendix in young patients are asymptomatic by themselves and incidental findings. They are not associated with neuroendocrine symptoms (carcinoid syndrome), which are only seen when retroperitoneal or liver metastases coexist. The frequency of NET of the appendix in children ranges from 0.085% to 0.169% of all histologically investigated appendical specimens and is therefore lower than in adults (Doede et al. 2000). Typical signs of acute appendicitis lead to appendectomy where besides local inflammation in about 30%, a visible yellowish tumor can be found. The majority of the appendical tumors however are diagnosed post surgery by histopathological examination. About 2/3 of the tumors are located at the tip of the organ, whereas only less than 8% are found at the basis.

Appendectomy is the treatment of choice, and most of the patients are sufficiently treated when the diagnosis was given. The tumor size is so far the most

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Table 33.1 German recommendations for therapy and follow-up of appendical NET in children (Redlich et al. 2009)

Therapy		
Tumor size		
≤15 mm, R0 resection		No further surgical therapy
≤15 mm, R1 resection		Local revision with lymph node sampling
>15 mm, R0 resection		Right hemicolectomy
>15 mm, R1 resection		Right hemicolectomy
Follow-up		
Year after diagnosis	Interval	
1	Quarterly	Physical examination, abdominal ultrasound, serum chromogranin, 5-HIAA in urine
2	Biannual	
3 to >10	Annual	

important parameter for predicting metastatic potential (Redlich et al. 2009; Thirlby et al. 1984); however, additional histopathological risk factors (infiltration of the mesoappendix, Ki-67 proliferation index, invasion of blood or lymph vessels, deepness of the infiltration of the appendical wall, and presence of mucin-producing cells) are under evaluation (Böger et al. 2009). Appendical NET can metastasize in the locoregional lymph nodes. In up to 35% of patients with tumors, >15 mm micrometastases in one or more removed lymph nodes can be found (Redlich et al. 2009). As a consequence, right hemicolectomy is suggested in these patients.

In general, totally removed tumors with a size below or equal to 15 mm are sufficiently treated with appendectomy alone. Patients with incomplete tumor resection should be re-operated. A local complete tumor resection with lymph node sampling of the locoregional nodes is the therapy of choice in these patients. For patients with tumors larger than 15 mm, a right hemicolectomy with lymph node resection is recommended. Since the NET of the appendix are slow-growing tumors, the re-operation can be electively planned after the initial symptoms of the acute appendicitis are cured and the patient and his parents agree in an informed consent to this procedure. There is no further need to extended invasive diagnostic or imaging. Chromogranin A in serum and 5-HIAA in urine can be determined; however, the predictive value of these parameters is still under discussion. Swollen lymph nodes in routinely performed ultrasound scans (mesenterial lymphadenitis) are very common in children with various virus infections of the gastrointestinal tract. Therefore, these findings in the follow-up should be interpreted very carefully.

The bearing of the micrometastases is not clear yet, and an association of appendical NET with other synchronous and metachronous malignant disease is reported (Sandor and Modlin 1998; Spunt et al. 2000). Therefore, a long-term follow-up for children and adolescents with appendical NET is recommended (Prommegger et al. 2002; Redlich et al. 2009).

References

Böger C, Vorwerk P, Leuschner I (2009) Clinopathological investigation of carcinoid tumors of the appendix in children and adolescent: is extended resection necessary? Eur J Pediatr 168:375-381

Doede T, Foss HD, Waldschmidt J (2000) Carcinoid tumors of the appendix in children – epidemiology, clinical aspects and procedure. Eur J Pediatr Surg 10(6):372–377

Lundqvist M, Wilander E (1987) A study of the histopathogenesis of carcinoid tumors of the small intestine and appendix. Cancer 60(2):201–206

Oberndorfer S (1907) Karzinoide Tumoren des Dünndarms. Frankf Zschr Pathol 1:426–432

Prommegger R, Obrist P, Ensinger C, Profanter C, Mittermair R, Hager J (2002) Retrospective evaluation of carcinoid tumors of the appendix in children. World J Surg 26(12): 1489–1492

Redlich A, Böger C, Boxberger N, Leuschner I, von Schweinitz D, Vorwerk P (2009) Neuroendocrine tumours (NET) of the appendix in children and adolescents - Results and recommendations of the GPOH-MET 97. In: 10th Congress of the European Paediatric Surgeons' Association, 56th Congress of the British Association of Paediatric Surgeons, Graz, 17–20 June 2009

Sandor A, Modlin IM (1998) A retrospective analysis of 1570 appendiceal carcinoids. Am J Gastroenterol 93(3): 422–428

Shaw PA (1991) The topographical and age distributions of neuroendocrine cells in the normal human appendix. J Pathol 164(3):235–239

Spunt SL, Pratt CB, Rao BN et al (2000) Childhood carcinoid tumors: the St Jude Children's Research Hospital experience. J Pediatr Surg 35(9):1282–1286

Stinner B, Rothmund M (2005) Neuroendocrine tumours (carcinoids) of the appendix. Best Pract Res Clin Gastroenterol 19(5):729–738

Thirlby RC, Kasper CS, Jones RC (1984) Metastatic carcinoid tumor of the appendix. Report of a case and review of the literature. Dis Colon Rectum 27(1):42–46

Gastrointestinal Stromal Tumors

34

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Contents

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34.1 Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract in adults but are very uncommon in children and adolescents. The exact incidence of GIST in this population has not been determined. In the three largest GIST series to date, the percentage of patients below the age of 21 ranged from 0.5% to 2.7%. There is a reported annual incidence of 6.5–14.5 per million cases of GIST overall, while the UK National Registry of Childhood Tumors has reported an annual incidence of 0.02 per million cases of GIST in children below the age of 14 years (Stiller 2007; Benesch et al. 2009).

34.2 Pathology and Biology

Until the 1980s, these tumors were classified as gastrointestinal leiomyomas or leiomyosarcomas. In 1983, Mazur and Clark proposed to term these neoplasms stromal tumors (Mazur and Clark 1983). Three morphological variants (epithelioid, spindle cell, and mixed cell) are distinguished (Corless and Heinrich 2008). Ultrastructural and immunophenotypic studies showed that GISTs share many morphological features with the interstitial cell of Cajal (ICC), a gastrointestinal pacemaker cell (Kindblom et al. 1998). In addition, ICC and the majority of GISTs stain positive for both CD34 and CD117 (KIT) (Corless and Heinrich 2008; Hirota et al. 1998). Expression of the cell surface transmembrane receptor KIT and, to a lesser extent, of the platelet-derived

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growth factor receptor alpha (PDGFRA) makes GISTs amenable to treatment with receptor tyrosine kinase inhibitors (RTKIs), such as imatinib, sunitinib, or nilotinib. Among adult cases, 95% and 70% of GISTs are positive for CD117 and CD34, and 60–80% carry gain-of-function mutations of the KIT gene, leading to its oncogenic activation (Corless and Heinrich 2008; Hirota et al. 1998). In contrast, only about 0–10% of pediatric GISTs have an oncogenic KIT mutation (Miettinen et al. 2005; Agaram et al. 2008; Janeway et al. 2007). Only two pediatric patients were reported with a mutation of the PDGFRA gene to date (Kuroiwa et al. 2005; Benesch et al. 2009). A significant expression of the insulin-like growth factor 1 receptor (IGF1R) in GISTs was recently reported (Agaram et al. 2008; Tarn et al. 2008).

34.3 Inheritance

GISTs occur either sporadically or rarely in association with other tumor predisposition syndromes (e.g., NF1) (Takazawa et al. 2005). The familial occurrence of GISTs has also been reported (Nishida et al. 1998). Phenotypic characteristics associated with familial GISTs include mastocytosis, dysphagia, cutaneous hyperpigmentation, multiple lesions, location in the small intestine and/or urticaria pigmentosa (Benesch et al. 2009). The association of gastric leiomyosarcoma, extra-adrenal paraganglioma, and pulmonary chondroma is termed Carney triad (Carney et al. 1977). An tumor predisposition syndrome comprising GISTs and paragangliomas ("Carney–Stratakis syndrome" or "Carney–Stratakis dyad") has to be separated from the "classic" Carney triad (Carney and Stratakis 2002). Recently, germline mutations encoding the succinate dehydrogenase (SDH) subunits B, C, and D have been identified in patients with Carney–Stratakis syndrome (McWhinney et al. 2007). Neither KIT, PDGFRA or SDH mutations were found in patients with Carney triad. The term familial GIST was originally used to refer to germline KIT mutations. Since GISTs are heritable in the case of either germline KIT or germline SDH mutations, these two forms of heritable GISTs have to be distinguished.

34.4 Symptoms

Although GISTs have been observed in newborns, most cases are diagnosed at the end of the first or during the second decade of life (Benesch et al. 2009). The average age of pediatric patients is 13 years, and there is a predilection for females of 2.5:1 (Benesch et al. 2009). Hypochromic, microcytic anemia, and anemia-related symptoms resulting from upper gastrointestinal bleeding are commonly observed at presentation. Nonspecific symptoms include loss of appetite, abdominal pain, nausea, vomiting, constipation, and diarrhea. The majority of pediatric GISTs are located in the stomach (typically in the antrum) (see Fig. 29.1), although GISTs are occasionally found in the small intestine, colon/rectum, omentum, and abdominal wall, with the tumor size ranging widely (1.5–35 cm) (Benesch et al. 2009). Multiple tumors or tumors with numerous satellite lesions are found in a considerable number of patients. Metastasis is not uncommon, and it typically presents in the liver (Fig. 29.2), lymph nodes, peritoneum, and mesentery; these lesions, however, rarely present at diagnosis (Benesch et al. 2009).

34.5 Diagnosis

Pediatric patients suspected of having GIST are worked up using the following: conventional abdominal radiographs, upper gastrointestinal contrast series, ultrasound, upper and lower endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (FDG-PET), angiography, fecal occult blood test, and labeled red cell scans. Gastrointestinal stromal tumors often present as either single or multiple well-circumscribed solid nodular masses. CT or MRI is mandatory both in the diagnostic work-up and follow-up of patients with GISTs (Benesch et al. 2009). FDG-PET is useful, particularly to monitor treatment response. Endoscopy is done in some patients, particularly in case of upper gastrointestinal bleeding, but endoscopic biopsies are often nondiagnostic. The final diagnosis is based on histology and immunohistochemistry. Tissue samples can be obtained either by biopsy or resection of the tumor. A tumor biopsy is unnecessary if the

tumor is localized and resectable. A road map pertaining to the diagnosis of GIST is presented in Fig. 29.5.

34.6 Treatment

Management guidelines for adult patients with GISTs have been presented by different groups (e.g., the GIST Task Force of the NCCN, ESMO) (Demetri et al. 2007; Casali et al. 2008) but are not available for children. Thus far, surgery is the mainstay of treatment aiming at local excision with microscopic free margins (Demetri et al. 2007; Casali et al. 2008). Removal of liver metastases may be indicated in selected cases. Since GISTs do not respond to conventional cytotoxic chemotherapy, its use is not recommended. Although RTKIs are increasingly used in the pediatric age group, the total number of reports on patients receiving imatinib and/or sunitinib for GISTs is still low (Agaram et al. 2008; Benesch et al. 2009; Janeway et al. 2009). Children with GISTs who are considered for treatment with RTKIs should be included into clinical trials. Otherwise, the patient's individual risk profile should be carefully assessed before RTKI treatment. In agreement with the guidelines for adult patients (Demetri et al. 2007; Casali et al. 2008), treatment with RTKIs is recommended only in children and adolescents with extensive GISTs (i.e., metastatic or initial R0 resection not feasible). Although there is no consensus on imatinib dosage, a starting dose of 400 mg/m^2 once daily might be suggested with a maximum dose of 400 mg BID. There are currently insufficient data to recommend adjuvant RTKIs treatment in R0-resected pediatric GISTs. Risk stratification in adult patients with GISTs is based on tumor size, mitotic index, and location of the primary tumor (Demetri et al. 2007; Casali et al. 2008). The risk stratification system has not been evaluated systematically in pediatric GISTs. The majority of patients with GISTs can be cured with complete surgical resection alone.

34.7 Prognosis

Prognosis is dismal if the tumor and/or metastatic lesions are not completely resectable (Benesch et al. 2009). However, even with extensive disease, some pediatric patients may have a prolonged and slowly progressing clinical course. Current evidence suggests that GISTs in the pediatric and adolescent population are different from those in adults. In adults, prognosis is determined by tumor size, mitotic activity, and location of the primary lesion. In the pediatric population, these three factors do not seem to be predictive of outcome. In general, pediatric GISTs tend to be less aggressive in nature, and despite recurrence of metastases, the clinical course is quite favorable in comparison to adults (Benesch et al. 2009).

34.8 Conclusion

Although additional clinical and long-term follow-up data have been recently reported by the German Cooperative Soft Tissue Sarcoma Group (CWS), data on the pathogenesis, clinical course, and prognosis of these tumors in this pediatric population are currently insufficient (Benesch et al. 2011). The soft tissue sarcoma registry of the CWS (CWS-SoTiSaR) is prospectively collecting data from children with soft tissue sarcomas and other rare soft tissue tumors, including GIST in Germany, Austria, Switzerland, Poland, and Sweden. Additionally, a European Working Group on Pediatric GISTs, in collaboration with the International Society of Pediatric Oncology (SIOP), was established.

References

Agaram NP, Laquaglia MP, Ustun B et al (2008) Molecular characterization of pediatric gastrointestinal stromal tumors. Clin Cancer Res 14:3204–3215

Benesch M, Wardelmann E, Ferrari A et al (2009) Gastrointestinal stromal tumors (GIST) in children and adolescents: a comprehensive review of the current literature. Pediatr Blood Cancer 53:1171–1179

Benesch M, Leuschner I, Wardelmann E, et al (2011) Gastrointestinal stromal tumours in children and young adults: a clinicopathologic series with long-term follow-up from the database of the Cooperative Weichteilsarkom Studiengruppe (CWS). Eur J Cancer 47(11):1692–1698, Epub 2011 Apr 10

Carney JA, Stratakis CA (2002) Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 108:132–139

Carney JA, Sheps SG, Go VL et al (1977) The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med 296:1517–1518

Casali PG, Jost L, Reichardt P et al (2010) Gastrointestinal stromal tumors: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl 5):ii98–102

Corless CL, Heinrich MC (2008) Molecular pathobiology of gastrointestinal stromal sarcomas. Annu Rev Pathol Mech Dis 3:557–586

Demetri GD, Benjamin RS, Blanke CD et al (2007) NCCN Task Force report: optimal management of patients with gastrointestinal stromal tumors (GIST) – update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 5(Suppl 2): S1–S29

Hirota S, Isozaki K, Moriyama Y et al (1998) Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279(5350):577–580

Janeway KA, Liegl B, Harlow B et al (2007) Pediatric KIT–wild-type and platelet-derived growth factor receptor alpha–wild-type gastrointestinal stromal tumors share KIT activation but not mechanisms of genetic progression with adult gastrointestinal stromal tumors. Cancer Res 67:9084–9088

Janeway KA, Albritton KH, Van Den Abbeele AD et al (2009) Sunitinib treatment of pediatric metastatic GIST after failure of imatinib. Pediatr Blood Cancer 52:767–771

Kindblom LG, Remotti HE, Aldenborg F et al (1998) Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 152:1259–1269

Kuroiwa M, Hiwatari M, Hirato J et al (2005) Advanced-stage gastrointestinal stromal tumor treated with imatinib in a 12-year-old girl with a unique mutation of PDGFRA. J Pediatr Surg 40:1798–1801

Mazur MT, Clark HB (1983) Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 7:507–519

McWhinney SR, Pasini B, Stratakis CA (2007) Familial gastrointestinal stromal tumors and germ-line mutations. N Engl J Med 357:1054–1056

Miettinen M, Lasota J, Sobin LH (2005) Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol 29:1373–1381

Nishida T, Hirota S, Taniguchi M et al (1998) Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet 19:323–324

Stiller C (2007) Childhood cancer in Britain: incidence, survival and mortality. Oxford University Press, New York, p. 104

Takazawa Y, Sakurai S, Sakuma Y et al (2005) Gastrointestinal stromal tumors of neurofibromatosis type I (von Recklinghausen's disease). Am J Surg Pathol 29:755–763

Tarn C, Rink L, Merkel E et al (2008) Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors. Proc Natl Acad Sci USA 105:8387–8392

Pancreatic Tumors

35

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35.1 Introduction

Pancreatic tumors in infancy and childhood are extremely rare. Even larger institutions can report only few cases over a time period of 20 and more years (Yu et al. 2009). Perez et al. identified 58 patients under the age of 20 years with malignant pancreatic tumors within the United States Surveillance, Epidemiology, and End Results registry (SEER, 1973–2004), accounting for an age-population-adjusted incidence of around 0.018 cases/100,000 in the United States (Perez et al. 2009). In the UK National Registry, 41 pancreatic tumors have been counted in 30 years (Brennan et al. 2004); the Italian TREP project identified 21 patients under the age of 18 years with malignant pancreatic tumors within a 10-year period (Dall'igna et al. 2010).

35.2 Differential Diagnosis

The differential diagnosis for malignant pancreatic tumors includes benign tumors as hemangiomas, cystic lesions like enterogenous cysts, pseudocysts, and abscesses. Also, tumors from adjacent organs like neuroblastoma, Wilms' tumor, and hepatoblastoma, as well as involvement of the pancreas in case of leukemia, lymphoma, or lymphoproliferative disorders, are more common than primary pancreatic tumors (Rebhandl et al. 2001). In case of a primary pancreatic tumor, pancreatoblastomas have to be considered especially under the age of 10 years, a solid-pseudopapillary Neoplasm (SPN) rather in female adolescents. Because of similar morphology, SPN might easily be confused with endocrine tumors. The pathology and clinical behavior of pancreatoblastoma and acinar cell

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Table 35.1 Differential diagnosis of pancreatic tumors in children and adolescents

Group	Entity
Malignant pancreatic tumors	Pancreatoblastoma
	Acinar cell carcinoma
	Ductal adenocarcinoma
Tumors with low malignant potential	Solid-pseudopapillary neoplasm
	Mucinous cystic neoplasm
	Inflammatory myofibroblastic tumor
Endocrine pancreatic tumors	Insulinoma
	Gastrinoma
	Others (VIPoma, glucagonoma, somatostatinoma)
Benign tumors	Hemangioma
	Teratoma (see chapter 39)
Tumor-like lesions	Cyst Local fibrous focus
	Pseudocyst
Congenital hyperinsulinism	
Secondary tumor manifestations	Lymphoma
	Rhabdomyosarcoma
	Primitive neuroectodermal tumor
	Neuroblastoma
	Hepatoblastoma
	Wilms' tumor

carcinoma are very similar, and differentiation between the two can be very difficult (Shorter et al. 2002). Anyway, acinar cell carcinoma as well as ductal adenocarcinoma is extremely rarely seen in children (Luttges et al. 2004; Perez et al. 2009) (Table 35.1).

35.3 Biology, Pathology, and Tumor Characteristics

35.3.1 Pancreatoblastoma

Pancreatoblastoma is the most common pancreatic tumor in children, accounting for approximately 25% of cases (Shorter et al. 2002). A joint analysis of the European Pediatric Rare Tumor Group (EXPeRT) collected 20 cases between 2000 and 2009 (Paper submitted). It mainly occurs in children under the age of 10 years and is rarely reported in neonates (mean age 4.5 years) (Defachelles et al. 2001; Shorter et al. 2002). Pancreatoblastomas have a bimodal age distribution: two-thirds of the cases occur in children and one-third in adults. Pediatric pancreatoblastomas show an incidence peak between second and third years of life (Klimstra et al. 1995). This embryonal tumor has many similarities with hepatoblastoma concerning age group, genetic alterations, and the response to chemotherapy. It shows alterations of the APC/β-catenin pathway and a loss of heterozygosity on chromosome 11p15.5 (Abraham et al. 2001). Pancreatoblastoma can be associated with Wilms' tumor, Beckwith–Wiedemann syndrome, and familiar adenomatous polyposis (Kerr et al. 2002; Antonello et al. 2009).

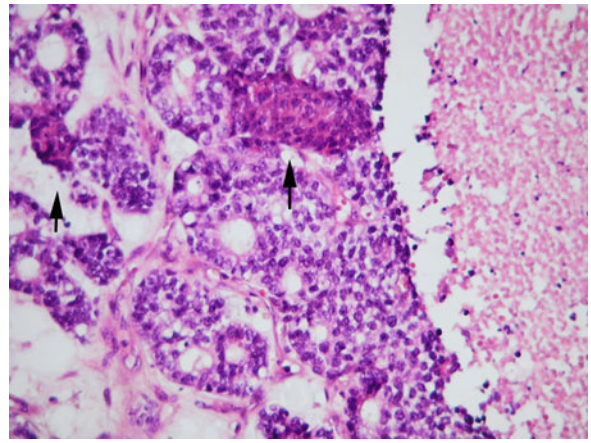

Fig. 35.1 Pancreatoblastoma with acinar-glandular features and with squamoid nests (*arrows*, H & E, ×400)

The tumor is frequently found in the pancreatic head or tail, well defined, and surrounded by a fibrous capsule (Dhebri et al. 2004). It is composed of cells showing predominantly acinar differentiation divided by septa. Neonatal pancreatoblastomas associated with Beckwith–Wiedemann syndrome are cystic (Kerr et al. 2002). Necrotic areas with calcifications are typical. The most important criterion for the histological diagnosis is the presence of squamoid nests (Fig. 35.1). Pancreatoblastomas may exhibit partially endocrine and ductal differentiation or even contain primitive components, somehow recapitulating the embryonic features of pancreas. The proliferative activity is between <1 and 42 mitoses/High power field (HPF). Nuclear polymorphism is low, and tumor cell invasion in perineural space and vessels is rare. The frequency of metastases in regional lymph nodes and liver has been reported to be between 17% and 50% (Dhebri et al. 2004; Perez et al. 2009). In most cases, expression and secretion of AFP can be observed and may serve as

tumor marker to follow the response of therapy (Saif 2007; Antonello et al. 2009).

35.3.2 Solid-Pseudopapillary Neoplasm (SPN)

Solid-pseudopapillary neoplasms (SPN) are rare tumors of the pancreas of low malignant potential mainly occurring in young females (10:1, mean age 22 years) (Papavramidis and Papavramidis 2005). SPNs were also known as "solid and papillary tumor," "solid-cystic tumor," "papillary cystic tumor," "solid and pseudopapillary epithelial neoplasm," "solid and cystic acinar cell neoplasm," and "Frantz tumor" (Kloppel et al. 1996; Papavramidis and Papavramidis 2005; Chung et al. 2006). Not seldom they were misdiagnosed as nonfunctioning islet cell tumors, adenocarcinomas, cystadenocarcinomas, or pseudocysts (Todani et al. 1988; Sclafani et al. 1991; Kloppel et al. 1996; Papavramidis and Papavramidis 2005; Chung et al. 2006). Recently, the tumor has been more recognized and therefore more often diagnosed, accounting for approximately 6% of all exocrine pancreatic tumors in all age groups (Papavramidis and Papavramidis 2005). In children, they account for 8–17% of all cases of pancreatic tumors (Grosfeld et al. 1990; Jaksic et al. 1992). Solid-pseudopapillary neoplasms are enigmatic tumors, with regard to their cell of origin and phenotype. SPNs are composed of unique cells which may exhibit epithelial, mesenchymal, and neuroendocrine features. During fetal development, there is a close relationship between the left genital ridge and the pancreatic anlage. It is speculated, therefore, that SPNs arise from pluripotent precursor cells from this area (Kosmahl et al. 2000). This would explain the female preponderance of >90%. In 95% of the cases, SPNs show an alteration of the APC/β-catenin signaling pathway and LOH on chromosome 5q22.1 (Antonello et al. 2009). In one-third of the SPNs, Fli-1 is over-expressed without exhibiting EWS/Fli-1 translocation, which is observed in pediatric tumors, mostly in Ewing sarcomas. The tumor localization is equally distributed in the pancreas (Rebhandl et al. 2001; Papavramidis and Papavramidis 2005). SPNs are often large tumors with a mean diameter of 6 cm (0.5–34.5 cm). The tumor consistency is soft with friable necrotic grey-hemorrhagic material in the center. Smaller tumors may be completely solid, mimicking endocrine neoplasms. Usually, the tumor is well demarcated and surrounded by a pseudo-capsule, which can be infiltrated by tumor cells (Fig. 35.2). This feature, however, is not a sign of malignancy in SPNs (Fig. 35.3). Histologically, the eponymous pseudopapillary appearance is found around the lacunae. Monomorphous polygonal tumor cells form solid areas or are arranged in pseudo-rosettes. The stromal component is often imperceptible, but it can be myxoid or sclerotic. The proliferation rate is very low (Rebhandl et al. 2001; Kosmahl et al. 2004). SPNs display a characteristic immunohistochemical pattern with expression of nuclear β-catenin, vimentin, CD56, and progesterone receptor (Fig. 35.4).

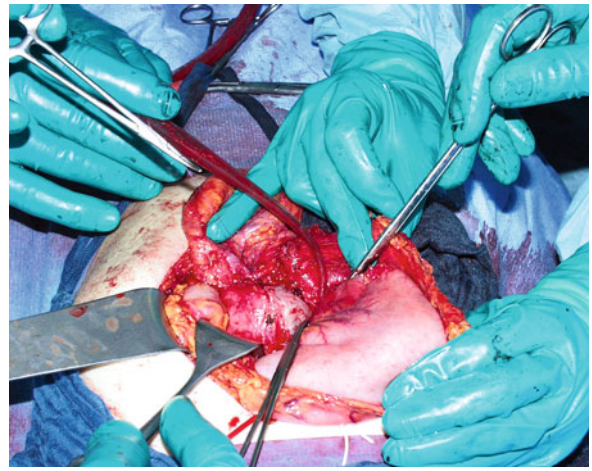

Fig. 35.2 Intraoperative view of a solid-pseudopapillary neoplasm (SPN) in the head of the pancreas in a 14-year-old female

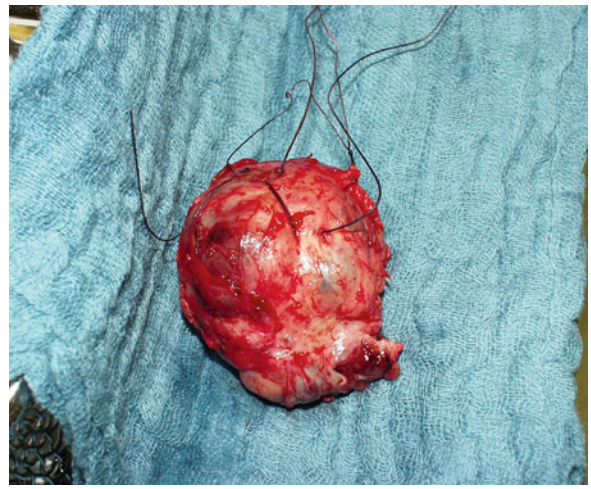

Fig. 35.3 Specimen of the SPN with free margins. Neither the pancreatic nor the choledochal duct has been touched

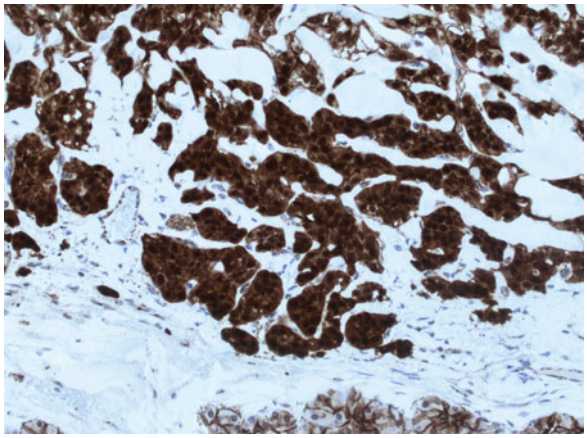

Fig. 35.4 Nuclear β-catenin expression in solid-pseudopapillary neoplasm. At the bottom, normal pancreatic acini with membrane-bound staining (×400)

Most SPNs (>90%) behave in a benign fashion. There are no established morphological criteria of malignancy which can be defined only by presence of metastases, mostly to the peritoneum or liver.

35.3.3 Endocrine Tumors and Congenital Hyperinsulinism

Pancreatic endocrine tumors, also called islet cell tumors, derive from any of the cell types of the islets, and may be benign (adenomas) or malignant (carcinomas), and occur equally often in male and female (Chung et al. 2006). They account for 1–2% of all pancreatic neoplasms at all age groups, but the prevalence is estimated to be much higher around 1/100,000. Insulinomas and gastrinomas arise either sporadically or, as in most pediatric cases, they are associated with multiple endocrine neoplasia (MEN) 1. Up to the fourth decade, gastrinomas develop in about 40% and insulinomas in 10% of all MEN 1 carriers. Additionally, adenomas are observed in the parathyroid gland in 90% and in the pituitary gland in 29% of the cases (Brandi et al. 2001). Other functionally active tumors like glucagonoma, VIPoma, and somatostatinoma are extremely rare. Hybrid tumors with characteristics of insulinoma and gastrinoma have been described (Lodish et al. 2008).

Insulinomas are solid tumors, approximately 1–3 cm in size, and well circumscribed (Bartsch et al. 2000). In contrast to the foci in congenital hyperinsulinism, they can be well distinguished macroscopically from normal pancreatic tissue (Figs. 35.5–35.9). Insulin and proinsulin expression can be shown by immunohistochemistry. In MEN 1, endocrine pancreatic tumors are frequently multifocal. Monohormonal endocrine cell clusters and microadenomas are well-defined precursor lesions of MEN-associated endocrine tumors.

The prognostic stratification of endocrine pancreatic tumors is based on tumor size, proliferation rate, angioinvasion, and infiltration of surrounding tissue (WHO 2000) (Table 35.2). The WHO classification from 2010 provided a more simplified system for risk stratification (WHO 2010) (Table 35.3). Malignancy is proven by metastases which arise in the regional lymph

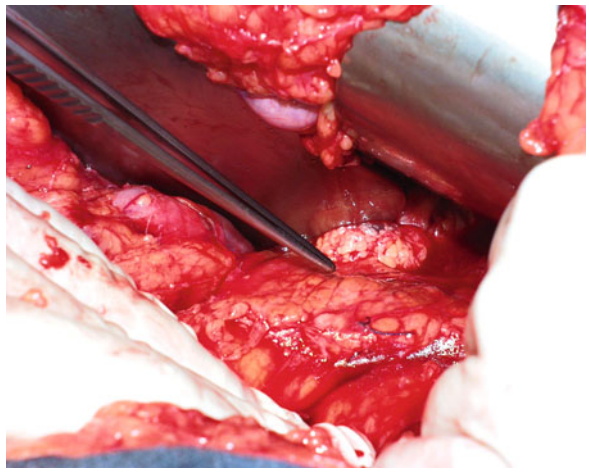

Fig. 35.5 Intraoperative view of an insulinoma (forceps tip) in the middle of the pancreas in a 16-year-old male with the MEN 1 syndrome

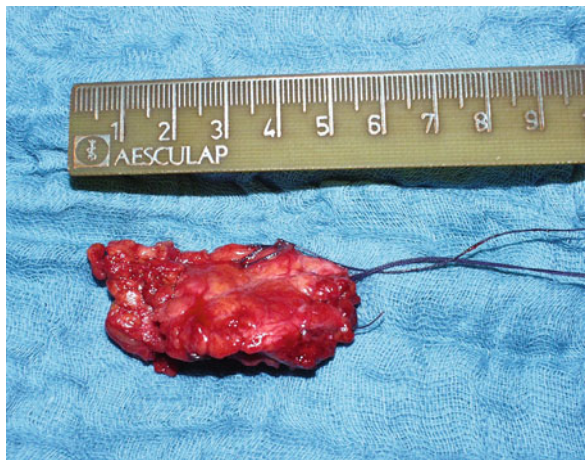

Fig. 35.6 Gross specimen of an insulinoma with free margins

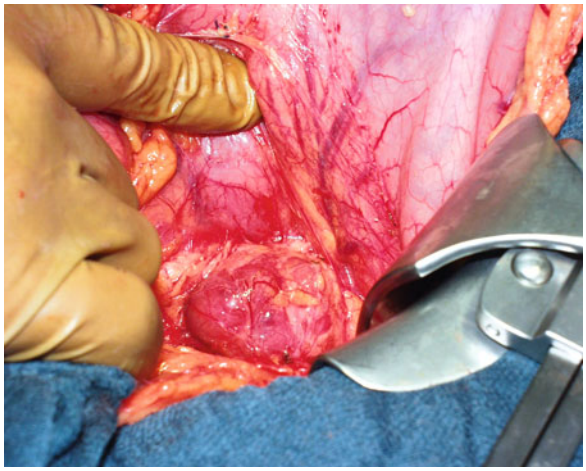

Fig. 35.7 Intraoperative view of an insulinoma in the middle of the pancreas in a 17-year-old female with the MEN 1 syndrome

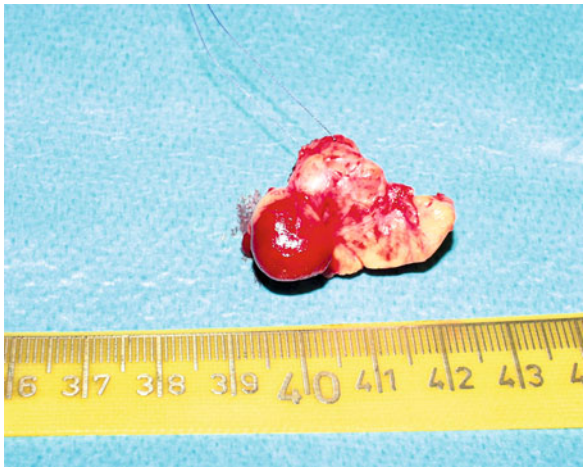

Fig. 35.8 Specimen of an insulinoma of a 14-year-old male with the MEN 1 syndrome

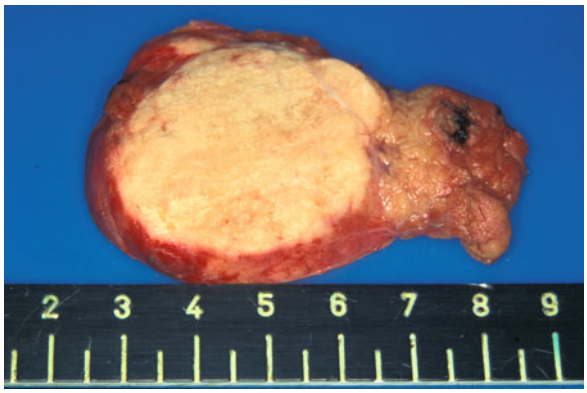

Fig. 35.9 Gross features of pancreatic endocrine neoplasm: well-circumscribed, *white-yellow* nodule without necrosis

Table 35.2 Classification of pancreatic endocrine tumors (Solcia et al. 2000, WHO 2000)

Well-differentiated endocrine tumor
Functioning
Insulin-producing (insulinoma)
Glucagon-producing (glucagonoma)
Somatostatin-producing (somatostatinoma)
Gastrin-producing (gastrinoma)
VIP-producing (VIPoma)
Others
Non-functioning
Microadenoma (<0.5 cm)
Others
Well-differentiated endocrine carcinoma
Functioning
Insulin-producing (insulinoma)
Glucagon-producing (glucagonoma)
Somatostatin-producing (somatostatinoma)
Gastrin-producing (gastrinoma)
VIP-producing (VIPoma)
Serotonin-producing with carcinoid syndrome
ACTH-producing with Cushing syndrome
Non-functioning
Poorly differentiated endocrine carcinoma – small- cell carcinoma
Mixed exocrine–-endocrine carcinoma
VIP, vasoactive intestinal peptide; ACTH, adrenocorticotropic hormone

Table 35.3 Recent classification of neuroendocrine neoplasms of the gastrointestinal tract including pancreas (WHO 2010)

Nomenclature	Features
1. Neuroendocrine Tumour Grade 1 (carcinoid)	Well-differentiated, Ki-67 Index <2%, < 2 mitoses / 10 HPF
2. Neuroendocrine Tumour Grade 2	Well-differentiated, Ki-67 Index <20%, < 20 mitoses / 10 HPF
3. Neuroendocrine Carcinoma	Poorly differentiated, small or large cell, Ki-67 Index >20%, >20 mitoses / 10 HPF
4. Mixed adenoneuroendocrine carcinoma (MANEC)	Epithelial and neuroendocrine components, at least 30% of either
5. Hyperplastic and preneoplastic lesions	

nodes and in the liver. In childhood, >90% of insulinomas are benign (Fig. 35.10).

In contrast, *gastrinomas* in MEN 1 usually include a malignant potential, and more than half of them have metastasized at the time of diagnosis (Brandi

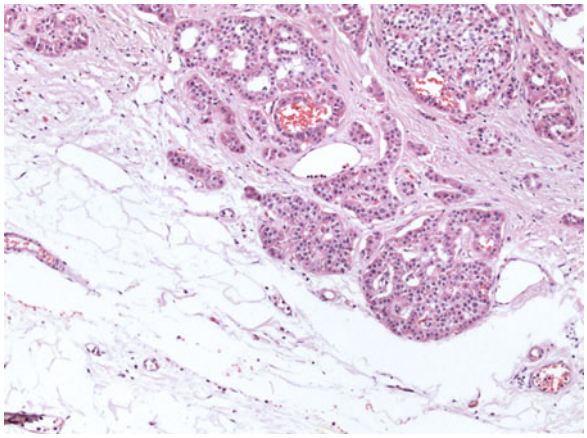

Fig. 35.10 Well-differentiated endocrine tumor composed of monomorphous round/oval cells arranged in nests (HE, ×200)

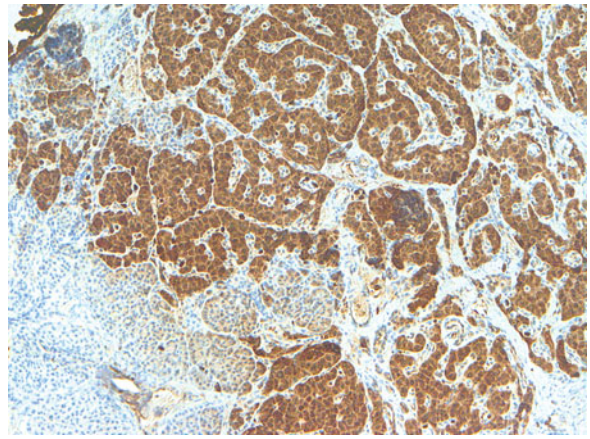

Fig. 35.12 Congenital hyperinsulinism (ancient name: nesidioblastosis) (IHC Proinsulin)

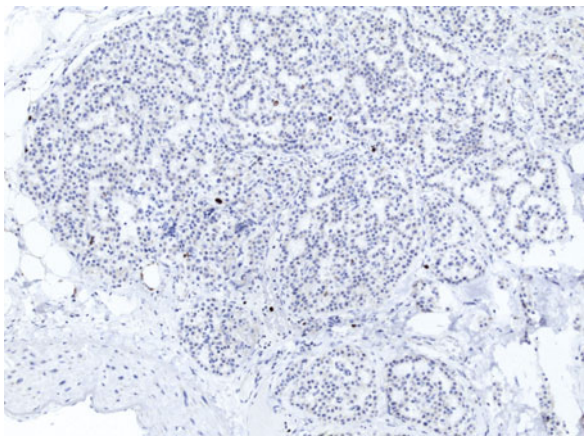

Fig. 35.11 Low proliferation rate in a well-differentiated endocrine tumor (Ki-67 immunostaining, ×200)

et al. 2001). Alike insulinomas, they are solid, well-defined encapsulated tumors (Fig. 35.11). Because of their malignant behavior, small size, multiplicity, and frequent localization in the duodenum, MEN-1-associated gastrinomas represent a diagnostic and therapeutic challenge (Norton et al. 2001).

35.3.3.1 Congenital Hyperinsulinism

Congenital hyperinsulinism – formerly called nesidioblastosis – is defined by morphologic changes in the endocrine pancreas causing hyperinsulinemic hypoglycemia in the absence of an insulinoma. Focal congenital hyperinsulinism is not a neoplastic lesion and represents the most important differential diagnosis of insulinoma. Congenital hyperinsulinism is caused by impaired control of insulin secretion from functionally defective pancreatic beta cells. The defect of the beta cells resides in the glucose recognition system. In most cases of focal congenital hyperinsulinism, there is a general paternal mutation of the K_{ATP} channels on the cellular level and a maternal loss of heterozygosity only in the cells of the focal lesion (deLonlay 2006). Morphologically, there is a diffuse or focal hypertrophy of beta cells (Anlauf et al. 2005) that are macroscopically not recognizable. The histological diagnosis is based on immunohistochemical detection of insulin in the hypertrophic Langerhans' islets (Fig. 35.12).

35.3.4 Acinar Cell Carcinoma (ACC)

Acinar cell carcinomas (ACC) arise from the exocrine acinar cells secreting the pancreatic enzymes. They show similarity to pancreatoblastomas harboring LOH on chromosome 11p in 50% of cases and alterations of the APC/β-catenin signaling pathway in 24% (Abraham et al. 2002). ACCs are large tumors at presentation, averaging 10 cm in diameter. Most ACCs are subdivided by large fibrotic septa and show pushing borders. Frequently, there is a nodular infiltration in the surrounding tissues and vessels. Necrotic areas are typical. Histologically, ACCs are solid but may exhibit a wide range of cell types: acinar, monotonous endocrine-like, trabecular, cystic, or even hepatoid differentiation (Sipos and Kloppel 2005). The mitotic activity is usually high (>50/10 HPF) (Abraham et al. 2002).

Immunohistochemically, pancreatic enzymes such as trypsin, chymotrypsin, and amylase are expressed in ACCs.

35.3.5 Ductal Adenocarcinoma

Ductal adenocarcinoma is the most frequent malignant pancreatic tumor in the adult age group, but is extremely rare in childhood (Grosfeld et al. 1990; Perez et al. 2009). Most cases date to the pre-immunohistochemical era and are usually not well documented. It has been speculated that in ancient reports, some SPNs or pancreatoblastomas had been misinterpreted as pediatric ductal adenocarcinoma (Shorter et al. 2002; Luttges et al. 2004). Nevertheless, according to the SEER registry, ductal adenocarcinomas of the childhood were associated with adverse outcome, exhibiting a 15-year-survival rate of 23% (Perez et al. 2009).

35.3.6 Benign Tumors

35.3.6.1 Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumors represent a range from truly mesenchymal tumors to reactive-inflammatory lesions. This enigmatic tumor consists of myofibroblasts admixed with inflammatory cells, predominantly with plasma cells and lymphocytes. The proliferation rate is low. It does not show a malignant behavior but is able to grow by infiltration. After incomplete resection, the rate of local recurrence is high (Mizukami et al. 2006).

35.3.6.2 Teratoma

Like in other locations, teratomas in the pancreas show components of all three germinal sheets (Mester 1990). Most of the cases published so far have been dermoid cysts (Kela 2008). Please also refer to Chap. 39 (Germ cell tumors).

35.3.6.3 Mucinous Cystic Neoplasm (MCN)

Mucinous cystic neoplasm is very rare in childhood. In adults, virtually all tumors arise in women located in the pancreatic corpus and tail. By imaging, it is difficult to distinguish from pseudocysts or other cystic tumors (Fukushima and Fukayama 2007). MCNs have no connection to pancreatic ducts. Microscopically, the solitary or multiple cysts are lined by tall, columnar epithelium with mucin secretion. The intra-cystic connective tissue resembles ovarian stroma by conventional histopathology and also by immunohistochemistry, exhibiting expression of estrogen and progesterone receptors as well as α-inhibin. In mucinous cystic neoplasms, the classical sequence from dysplasia and adenoma to carcinoma is well known. This is associated with a loss of tumor suppressor genes Smad4 and p53 and an increasing frequency of K-ras oncogen mutations (Fukushima and Fukayama 2007; Garcea et al. 2008). In children, no malignant transformation has been reported to date.

35.3.6.4 Fibrous Focus

Chronic pancreatitis can result in circumscribed fibrotic indurations in the pancreas which may mimic a tumor. Pancreatitis in childhood can originate from cholelithiasis, choledochal cysts, pancreas divisum, medication, metabolic diseases, hemolytic-uremic syndrome, viral diseases (mumps and coxsackie), and hereditary chronic pancreatitis of childhood with mutations in the PRSS1 gene (Chung et al. 2006; Rebours et al. 2009). Hereditary pancreatitis is frequently associated with an adenocarcinoma of the pancreas later in life.

35.3.6.5 Pancreatic Pseudocysts

Pancreatic pseudocysts are by far the most common cystic lesions in the pediatric pancreas. In most cases, they originate from blunt abdominal trauma, rarely from chronic pancreatitis.

35.4 Diagnosis of Pancreatic Tumors

35.4.1 Clinical Presentation

Pancreatic tumors in children normally present with a palpable mass, abdominal pain, or general symptoms like weight loss, fatigue, and mild gastrointestinal problems (Lack et al. 1983; Klimstra et al. 1995; Shorter et al. 2002). As tumors can arise at any site within the pancreas and origin from the ductal epithelium is rare, jaundice is less often seen in adults (Lack 1989; Shorter et al. 2002). Many cystic tumors are incidentally discovered, some after blunt abdominal trauma (Rebhandl et al. 2001). Most children with a pancreatic malignancy present with advanced tumors. In case of a tumor arising from the head of the pan-

Table 35.4 Diagnostic strategy in pediatric pancreatic tumors

Procedure	Specific questions
Clinical assessment	
Physical examination	Mostly mild and unspecific (gastrointestinal) symptoms, but also signs of obstruction of duodenum, gastric outlet, biliary tract or venous obstruction, palpable mass
Laboratory assessment	
– Hepatic function: Bil (dir. + indir.), AP, γ-GT, GOT, GPT, total protein, albumin	Elevated in case of obstructive jaundice
– Calcium, parathormone, prolactin, chromogranin A, and a hormone profile including insulin, proinsulin, VIP, gastrin, somatostatin, glucagon	In case of suspected endocrine active tumor
– LDH, amylase, lipase	Unspecific marker
– AFP	Pancreatoblastoma
– NSE	Sporadically elevated in SPN
– CA 19.9	Pancreatic ductal adenocarcinoma, sporadically elevated in SPN; not suitable to detect early stages, may be used to monitor for cancer recurrence; also elevated in chronic pancreatitis, benign obstructive jaundice, cystic lesions
– CEA	Assists with evaluating pancreatic cysts as benign or malignant
– CA 125	Pancreatic ductal adenocarcinoma
– Pancreatic oncofetal antigen	Pancreatic ductal adenocarcinoma
– Catecholamines	Exclusion of neuroblastoma, sporadically elevated in SPN
– Blood count	Exclusion of hematologic malignancy
Radiographic assessment	
Abdominal ultrasound and MRI	Tumor size, localization and tumor borders, consistency, presence of cystic and solid components, necrosis, calcification, hemorrhage, dilatation of the pancreatic and bile duct, local and vascular infiltration, ascites, lymphadenopathy, and liver metastases
Abdominal CT and MRI	Site, tumor size, organ of origin, cystic structures or calcification, ascites, obstruction, or invasion of other organs
Chest CT	Lung metastases
CNS MRI	CNS metastases
Bone scan	Skeletal metastases
Histologic assessment	
See above for details	Classification according to WHO
Genetics	
MEN 1	Gastrinoma
KRAS2 gene	Ductal adenocarcinoma
PRSS1 gene	Familial chronic pancreatitis
Other assessments	
Secretin test	In case of suspected gastrinoma
Fasting blood glucose	In case of endocrine active tumor
Screening methods	
Screening tests	Not available, currently ongoing research: e.g., Johns Hopkins Medicine (http://pathology.jhu.edu/pc/BasicScreening.php?area=ba)

creas, the patient might present with mechanical obstruction of the duodenum and gastric outlet, jaundice, and gastrointestinal bleeding. However, these symptoms are rare in childhood, most likely due to the soft consistency of the tumors. Varices, hemorrhage, and ascites, possibly resulting in hepatic failure, may be seen due to venous obstruction (Pappo and Furman 2006). In case of acinar cell carcinoma, painful, subcutaneous nodules and polyarthritis might be seen, which is caused by elevated lipase secretion by the tumor (Klimstra et al. 1992). Functioning endocrine tumors may produce hormones and lead to specific symptoms

related to the active hormone being produced. In case of insulinoma, hypoglycemic symptoms, which might manifest as weakness, fatigue, change in behavior, confusion, seizures, or coma, are seen (Field 1993). Blood glucose levels under 50 mg/dl, hypoglycemia in case of fasting, and immediate disappearance of symptoms with intravenous administration of glucose are typical symptoms. Serum insulin levels are elevated with a higher proportion of proinsulin (Field 1993). Gastrinoma causes the Zollinger–Ellison syndrome with gastric hyperacidity, multiple and recurrent peptic ulcers in uncommon locations, gastroesophageal reflux, and diarrhea (Zollinger 1987). Another functioning islet cell tumor exceedingly rarely seen in children is the VIPoma causing Verner–Morricon syndrome (massive watery diarrhea, hypokalemia, and achlorhydria) (Grosfeld et al. 1990; Chung et al. 2006) (Table 35.4).

35.4.2 Laboratory

In pancreatic tumors in childhood, the routine laboratory tests are of little value. Often there are no abnormal laboratory findings, no evidence of pancreatic insufficiency, cholestasis, impaired liver function, or endocrine syndrome. Even lactate dehydrogenase in the serum is rarely elevated. Anyway, alpha-fetoprotein (AFP) is increased in 68% of cases of pancreatoblastoma and can serve as a tumor marker. In case of solid-pseudopapillary neoplasm, elevated serum levels of neuron-specific enolase (NSE) and CA 19.9 as well as elevation of urinary vanillylmandelic and homovanillic acids have been reported in sporadic cases (Casanova et al. 2003).

If cystic lesions are present, the differential diagnosis between pseudocysts, true cysts (von Hippel–Lindau, cystic fibrosis, and lymphoepithelial cyst), and cystic tumors (SPN, cystic pancreatoblastoma, and cystic teratoma) can be very difficult (Correa-Gallego et al. 2010). Pseudocysts are the most frequent cystic lesions encountered (70%) (Singhal et al. 2006). A cystic tumor can be suspected if there is no history of pancreatitis or blunt abdominal trauma; if the cyst has thick walls, septa, and lobuli; if there is no connection to the pancreatic duct; and if cystic fluid shows low level of amylase (Chung et al. 2006). The detection of elevated tumor markers like CEA and CA 19.9 in the cystic fluid shows low sensitivity and high specificity.

If an endocrine active tumor is suspected, fasting blood glucose and MEN-1-associated parameters calcium, parathormone, prolactin, chromogranin A, and a hormone profile including insulin, proinsulin, VIP, gastrin, somatostatin, and glucagon should be assessed. In suspected gastrinoma, a secretin test is performed.

35.4.3 Imaging

The first-line tool is ultrasonography on suspicion of a pancreatic mass. Tumor size, localization and tumor borders, consistency, presence of cystic and solid components, necrosis, hemorrhage, dilatation of the pancreatic and bile ducts, local and vascular infiltration, lymphadenopathy, and liver metastases can be demonstrated (Montemarano et al. 2000). The value of sonography, however, largely depends on the personal experience of the examiner. Anyway, the examination of the pancreas by ultrasonography is often impaired by air superposition in the bowel, so that CT or MRI may be of assistance regarding localization, extension of the lesion, and presence of metastases. In the case of suspected pancreatoblastoma, CT or MRI is mandatory for precise staging. However, lymph node metastasis or duodenal or vascular infiltration by the tumor may be missed even using up-to-date imaging methods (Montemarano et al. 2000; Chung et al. 2006). A preoperative ERCP or MRCP is indicated if there is a dilatation of the bile or pancreatic duct.

The value of the ^{18}Fluorodeoxyglucose-PET-CT for the diagnosis of a pediatric pancreatic tumor is not known so far. In the adult age group, the ^{18}F-PET-CT was able to distinguish between malignant and benign pancreatic lesions (Herrmann et al. 2008). If endocrine tumors are clinically suspected, PET-CT with new, innovative tracers (^{18}F-L-DOPA, ^{68}Ga-DOTATOC, and ^{11}C-5-Hydroxytryptophane) has been giving promising results (Orlefors et al. 2005; Kauhanen et al. 2007; Tessonnier et al. 2010). If congenital hyperinsulinism is suspected, an ^{18}F-L-DOPA-PET-CT is able to distinguish between diffuse and focal forms and in the latter case to localize the focus exactly (Barthlen et al. 2008).

Skeletal scintigraphy is indicated for pancreatoblastoma to look for bone metastasis. If an endocrine tumor is suspected, a somatostatin receptor scintigraphy (^{111}In-DTPA-DPhe-octreotide) can aid to establish the diagnosis and localize the tumor. Especially for gastrinomas which are often small, multiple, and submucous

Table 35.5 Imaging characteristics of pancreatoblastoma and solid-pseudopapillary neoplasm

Pancreatoblastoma	Solid-pseudopapillary neoplasm
– Child <10 years	– Young female adolescent
– Well-defined, solitary lesion in the pancreas of considerable size	– Usually large, well circumscribed
– Half of the cases occurring in the head of the pancreas	– Equally distributed over the pancreas
– Heterogenous tumor with septa and few calcifications, hemorrhagic and necrotic areas, simultaneous solid and cystic areas	– Heterogenous tumor with simultaneous occurrence of solid, cystic, hemorrhagic, and necrotic areas in the tumor; calcification in the tumor capsule
– Metastasis in regional lymph nodes and liver (up to 50%)	– No metastasis
– Well-vascularized tumor without hemorrhage	– Well-vascularized tumor with hemorrhage
– Rare dilatation of the choledochal duct	– Very rare dilatation of the choledochal duct
– Fibrous capsule	– Thick, fibrous tumor capsule
– Often compressing nearby organs without invading them	– Compression of adjacent structures is more often seen than invasion

in the duodenal wall, the somatostatin receptor scintigraphy became an important diagnostic tool (Norton et al. 2001; Yeung and Pasieka 2009). Functional localization of gastrinomas, measuring gastrin gradients, is performed by hepatic venous sampling after the selective intraarterial injection of secretin (Norton et al. 2004) (Table 35.5).

35.4.4 Biopsy

In most cases of a pancreatic tumor in childhood, it will be impossible to establish a diagnosis from imaging alone. There have been cases of pancreatoblastoma which have been misinterpreted as intraperitoneal cysts prenatally (Sugai et al. 2006). In principle, a tumor biopsy would be advantageous before making a decision for therapy. This biopsy could be done by fine-needle aspiration (Nadler et al. 2002), by laparoscopy (Metzelder et al. 2007), or by open incision. In fine-needle aspiration, however, the amount of tissue obtained is often very small. A definitive diagnosis is difficult to establish, especially concerning the heterogeneity of most pancreatic tumors in childhood. Biopsy by laparoscopy for diagnostic purposes is a well-accepted strategy in pediatric surgery (Metzelder et al. 2007). However, the assessment of resectability of a pancreatic tumor by laparoscopy is by far more difficult than by the open approach. The risk of misinterpretation, therefore, is increased and the chance of a complete healing in the first step is decreased. Additionally, there is the possibility of tumor cell spillage by the CO_2 insufflation. A tight closure of the tumor capsule after the biopsy by laparoscopy is technically demanding. Several cases of local or disseminated peritoneal recurrences of an SPN after laparoscopic biopsy have been reported, even in case of clear margins in initial resection (Fais et al. 2009). Therefore, and with the exception of small, localized tumors in the pancreatic tail which can be resected by laparoscopy, a primary open approach for the definite diagnosis and treatment of pancreatic tumors in childhood and adolescence of unknown biological behavior is strongly recommended.

35.4.5 Staging

The TNM staging system is not used for the very heterogeneous group of pediatric pancreatic and endocrine tumors, and currently no other staging system is in common use (AJCC 2006). Anyway, for endocrine tumors, the WHO classification combines different clinical prognostic factors to differentiate between well-differentiated endocrine tumors with benign or uncertain behavior, well-differentiated endocrine carcinoma, and poorly differentiated endocrine carcinoma (see Table 35.3). In most cases, they are endocrinally active, though with more advanced diagnostical and surgical methods, the percentage of nonfunctioning islet cell tumors has risen in the last 10 years (Anlauf et al. 2005). The active polypeptide can produce clinical symptoms (functioning or hyperfunctioning islet cell tumors) or not (nonfunctioning or clinically silent tumor). Functioning islet cell tumors are further classified into insulinomas, glucagonomas, somatostatinomas, gastrinomas, and vasoactive intestinal polypeptide tumors according to the hormone they produce (see also Table 35.4). In case of production of more than

one hormonally active peptide, clinical symptoms are related to one hormone being predominant. Under all types of functioning islet cell tumors, insulinoma (47%) and gastrinoma (30%) are most often seen (Chung et al. 2006). Microadenomas are tumor nodules with a diameter of less than 0.5 cm, which is the minimum size required for gross detection.

35.5 Treatment of Pancreatic Tumors

Though treatment strategies for pancreatic tumors in children mainly have to be derived from experience in adults, more and more experience is available to understand specific treatment approaches for children and adolescents. The treatment mainly relies on complete resection as most tumors are considered to be not or a little radio- or chemosensitive (Pappo and Furman 2006). An exception seems to be pancreatoblastomas that proved to be sensitive to chemotherapy (Klimstra et al. 1995; Murakami et al. 1996; Chun et al. 1997; Defachelles et al. 2001). Anyway, metastases might occur in several entities, and systemic therapy therefore has to be considered.

35.5.1 Surgical Therapy

With the rare exception of unequivocally proven unresectability and metastasis, all pancreatic tumors must be treated surgically in curative intention. The surgical procedure depends on the malignancy of the tumor and the location. In case of a tumor of the tail or body, a distal pancreatic tail resection with preservation of the spleen can be performed. This can be done conveniently by a laparoscopic approach. The standard surgical procedure for tumors of the head of the pancreas is the Whipple procedure (partial pancreatoduodenectomy), although a less radical resection like pylorus-sparing partial pancreatoduodenectomy (Traverso-Longmire), partial pancreatic resection, or even enucleation might be more adequate in some cases. Patients also seem to profit from tumor debulking in case of unresectability.

35.5.1.1 Surgical Approach

After a transverse laparotomy, the omental bursa is opened, and the situation is evaluated:

- Is an enucleation or a local resection of the tumor possible?
- Is there evidence of peritoneal infiltration or of local or liver metastasis?
- Is there evidence of an infiltration of the duodenum, the choledochal duct, the porta hepatis, the caval vein, or the superior mesenteric vessels?

If the tumor seems to be resectable, it should be removed totally even without knowledge of the histological diagnosis (Perez et al. 2009; Snajdauf et al. 2009). Open biopsy should only be performed in all cases that would necessitate extended surgery (e.g., partial duodenopancreatectomy) for complete resection. The final histopathological diagnosis should be awaited. Frozen sections are valuable for detection of residual tumor cells in the resection margins. However, final diagnosis may not be achieved in all cases because of the necessity of additional immunohistochemical examination in certain tumors (SPN vs. endocrine; pancreatoblastoma/ACC vs. endocrine) Intraoperative tumor cell spillage, however, must be strictly avoided. The tumor capsule must be closed carefully after the biopsy.

35.5.2 Therapy and Prognosis of Specific Entities

35.5.2.1 Pancreatoblastoma

Patients with pancreatoblastoma have good chances for cure if radical resection of all vital tumor tissue is performed (Brennan et al. 2004; Saif 2007; Perez et al. 2009; Yu et al. 2009). In most cases, the tumor is located ventrally in the pancreatic head, surrounded by a capsule and has no connections to the duct system. Therefore, a local resection without mutilating surgery is possible in many cases, achieving tumor-free margins (Dhebri et al. 2004). Radical lymph node dissection is necessary in every case because the prognosis of the patients gets worse if a lymph node metastasis develops after tumor resection (Dhebri et al. 2004). If R0 resection has been achieved and serum AFP level is normal, no further therapy and close clinical follow-up are indicated. Anyway, surgical intervention should be performed only by experienced surgeons who are familiar with the technique of partial duodenopancreatectomy as well. The pylorus-preserving strategy of Traverso-Longmire has to be preferred because the quality of life is significantly better than that after a classical Whipple operation.

Though the mainstay of treatment is complete surgical resection, patients often present with metastases and/or unresectable tumor at the time of diagnosis, and

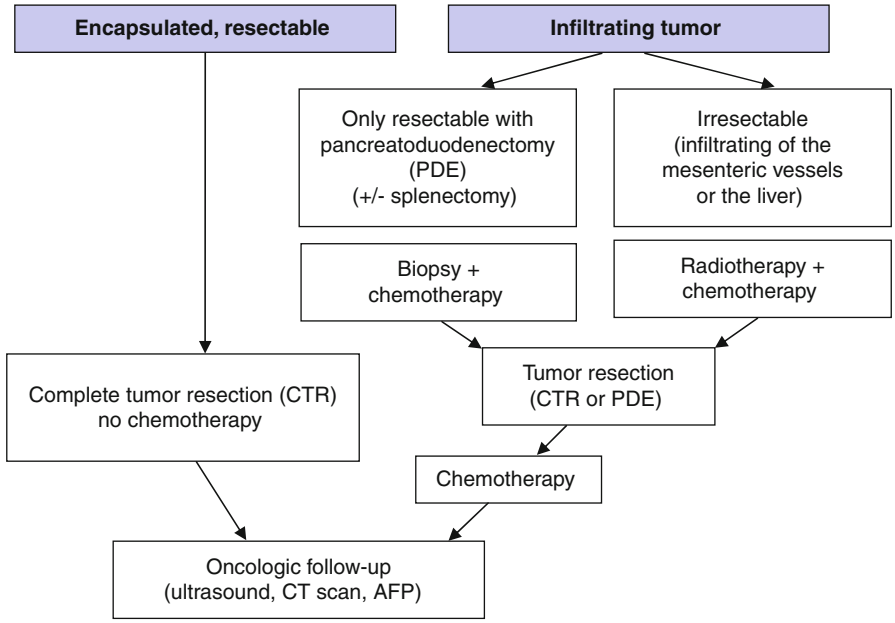

Fig. 35.13 Possible treatment regimen for encapsulated and infiltrating pancreatoblastomas as presented by Vossen et al. (1998)

therefore preoperative chemotherapy treatment might be needed and in fact has lead to marked tumor reduction in several cases (Defachelles et al. 2001). Anyway, the most effective chemotherapy for pancreatoblastoma is not known, and a variety of different regimes have been used so far (Dhebri et al. 2004). The PLADO regime (cisplatin and doxorubicin) as recommended for hepatoblastoma in the SIOPEL study (Ogawa et al. 2000; Perilongo et al. 2000) or a combination of cisplatin, etoposide, ifosfamide, and adriamycin might be considered for treatment (Vossen et al. 1998) (Fig. 35.13). So far, it is not known whether chemotherapy results in improved survival rates and whether adjuvant chemotherapy is successful in resected cases (Shorter et al. 2002). Also, the role of radiotherapy remains unclear though response to irradiation in case of recurrent or incompletely resected pancreatoblastoma has been reported (Griffin et al. 1987; Murakami et al. 1996; Defachelles et al. 2001). Surgical resection of liver metastases should be considered (Grosfeld et al. 1990; Murakami et al. 1996).

35.5.2.2 Prognosis

Approximately one-third of the reported cases of all age groups present with metastases to the liver and abdominal lymph nodes and less common to the lung, brain, and peritoneum (Klimstra et al. 1995; Imamura et al. 1998; Gupta et al. 2000; Montemarano et al. 2000). While in adults pancreatoblastoma is reported to be fatal, especially in case of metastases and unresectability (Dhebri et al. 2004), the tumor seems to behave less aggressively in pediatric patients, showing a better outcome (5-year-survival 50%) (Kohda et al. 2000; Defachelles et al. 2001; Saif 2007). The latest analysis of the EXPeRT group even reported a 5-year event-free survival and overall survival of 58.8% and 79.4%, respectively. Outcome did not correlate with tumor site and size but was influenced by tumor stage and by the feasibility of complete resection. The response rate to chemotherapy was 73% (Bien et. al 2011). Long-term survival after response to radiation and chemotherapy in case of metastatic disease is reported (Griffin et al. 1987; Vannier et al. 1991; Klimstra et al. 1995; Murakami et al. 1996; Vossen et al. 1998; Ogawa et al. 2000; Dhebri et al. 2004). Anyway, recurrence is common (60%) even after complete surgery; therefore, close follow-up is necessary (Shorter et al. 2002).

35.5.2.3 SPN

Specific treatment experience for children does not exist. Because of the low grade of malignancy of SPNs and the existence of a fibrous capsule, an enucleation of the tumor might be sufficient, especially in pediatric cases (Grosfeld et al. 1990; Matsunou and Konishi 1990; Jaksic et al. 1992; Wunsch et al. 1997). But as metastatic and local recurrence does occur in case of incomplete resection or enucleation, complete resection

with save margins should be the aim (Todani et al. 1988; Sclafani et al. 1991; Klimstra et al. 2000; Zhou et al. 2001; Papavramidis et al. 2005). If the tumor is not excised completely, the rate of local recurrence is very high (73%), and the almost 100% survival rate after R0 resection decreases dramatically (Campanile et al. 2011). Papavramidis et al. reported that complete resection of SPN was achieved by local excision in 22%, by pancreatic tail resection in 40%, by a Whipple resection in 22%, and by a Traverso-Longmire partial duodenopancreatectomy in 4% of the cases (Papavramidis et al. 2005). Anyway, radical local approaches or extensive lymphatic dissection are not necessary, and tumor size, recurrence, and limited metastases as well as local invasion (for example, into the portal vein or superior mesenteric artery) should not lead to the conclusion of unresectability (Jeng et al. 1993; Martin et al. 2002). Some of these patients can survive more than 10 years after surgery (Kaufman et al. 1986; Nishihara et al. 1993a; Mao et al. 1995; Papavramidis et al. 2005).

If a central pancreatic resection has to be performed, the drainage of the tail must be accomplished by a Roux-en-Y jejunal loop or a pancreaticogastrostomy (Fisher et al. 2007). If the portal vein, the mesenteric vein, or the venous confluens are infiltrated, a bypass can be constructed using jugular vein graft or a Goretex graft (Goh et al. 2007; Sperti et al. 2008). The spleen should be preserved in childhood in any case to avoid the overwhelming post-splenectomy infection (OPSI) syndrome.

Laparoscopic tumor biopsy is not recommended in suspected SPN because of the risk of tumor cell spillage (Fais et al. 2009). Surgical treatment for metastases should be considered, especially single liver metastases often can be resected (Nishihara et al. 1993b; Ogawa et al. 1993; Panieri et al. 1998; Klimstra et al. 2000; Saiura et al. 2000; Martin et al. 2002). Patients profit from debulking if complete resection is not possible (Todani et al. 1988; Sclafani et al. 1991; Nishihara et al. 1993a; Mao et al. 1995; Wang et al. 1998; Papavramidis et al. 2005). In case of a local recurrence of an SPN, even multiple resections may be of value because the overall prognosis of this slowly growing tumor is excellent (Tipton et al. 2006; Goh et al. 2007; Perez et al. 2009). The role of chemotherapy and radiotherapy in SPT is not known. Rebhandl et al. report successful postoperative treatment of a pediatric patient with metastasized SPN with ifosfamide, cisplatin, and VP16 (Rebhandl et al. 2001). Gemcitabine (Maffuz et al. 2005) and a combination of cisplatin and 5-fluorouracil (Strauss et al. 1993) have been successfully used as preoperative chemotherapy regime in two adult patients with unresectable SPN. Also, radiotherapy might be of value in cases of unresectable tumors (Fried et al. 1985; Matsunou and Konishi 1990; Rebhandl et al. 2001).

As diagnosis might not be established until intraoperative frozen section biopsy, the surgeon and pathologist should be aware of this entity as correct diagnosis might lead to a different surgical approach in case of SPT.

35.5.2.4 Prognosis

Unlike other malignant pancreatic tumors occurring in children, solid-pseudopapillary neoplasms show a slow-growing, low malignant behavior and therefore have an excellent prognosis with surgery alone. Approximately 85% of the patients present with local disease (Mao et al. 1995; Wang et al. 1998; Klimstra et al. 2000), and 95% of these patients can be cured by complete surgical excision (Kaufman et al. 1986; Mao et al. 1995; Papavramidis et al. 2005). In the case of recurrence (6.6%) tumor spread to liver or peritoneum and more rarely to lymph nodes, lung and skin are seen (Rebhandl et al. 2001; Papavramidis et al. 2005). In single cases, repeated surgery for local recurrence and metastasis has proved to be of value (Rebhandl et al. 2001). Metastases occur late (average disease-free survival of 8.5 years) (Gonzalez-Campora et al. 1995; Lam et al. 1999) and are seen more often in older women (Todani et al. 1988; Matsunou and Konishi 1990; Nishihara et al. 1993a; Wang et al. 1998; Zhou et al. 2001). Anyway, until now it is not known if prognosis in children is different from prognosis in adults as specific survival data do not exist.

35.5.2.5 Endocrine Tumors

While 90% of insulinomas are benign, this is the case for only 40% of gastrinomas and 20–30% of glucagonomas (Grosfeld et al. 1990). Large tumors might have metastasized at the time of diagnosis, and metastases may also occur many years after diagnosis (Buetow et al. 1995). Different parameters for prediction of biological behavior and outcome have been found: tumors larger than 2–3 cm, tumor necrosis, well-differentiated tumors, vascular and perineural invasion, high mitotic count, high proliferation, and tumor biology (insulinoma vs. non-insulinoma) have

been strongly correlated with malignant behavior (Donow et al. 1990; La Rosa et al. 1996; Hochwald et al. 2002).

The short-term therapy of insulinoma is to prevent severe hypoglycemia including administration of high-dose glucose i.v. and glucagon and octreotide s.c. In case of gastrinoma, conservative therapy to alleviate symptoms consists of oral PPI. The best long-term survival has been seen in case of complete surgical resection, absence of liver metastases, or aggressive treatment of them, if present (Chu et al. 2002); 90% of insulinomas and most gastrinomas present as solitary mass and therefore can be cured by complete resection alone (Service et al. 1991). Usually, insulinomas are well circumscribed and can be enucleated without touching the pancreatic duct. If an insulinoma is located in the pancreatic tail, a spleen-preserving left resection is indicated. It can be completed, if necessary, by enucleation of additional tumors in the pancreatic corpus or head (Bartsch et al. 2000). If insulinoma cannot be localized, intraoperative ultrasound should be performed.

In case of MEN 1, therapy is complicated by often multiple pancreatic neuroendocrine tumors (Service et al. 1991; Mergo et al. 1997). Therefore, during surgery, the pancreas must be carefully scrutinized with inspection, bimanual palpation, and intraoperative sonography from the uncinate processus to the tip of the tail in order to find and resect all existing tumors. A systematic lymphadenectomy like in pancreatoblastoma, however, is not routinely recommended in insulinoma.

As most of the gastrinomas occur in the so-called gastrinoma triangle around the head of the pancreas, resection for gastrinoma has to involve this area (Machado et al. 2001). As long as additional gastrinomas in the duodenum are excluded, a duodenopancreatectomy is not necessary in most cases (Bartsch et al. 2000; Brandi et al. 2001). A duodenotomy, however, is performed as a routine since duodenal gastrinomas frequently escape preoperative imaging (Norton et al. 2004). MEN-1-associated gastrinomas present multiple, small nodules in the duodenum. Therefore, duodenotomy with transillumination is mandatory (Norton et al. 2004). However, the role of surgery is controversial in MEN-1-associated gastrinoma because complete cure by surgery is extremely rare.

Lymph node metastases are frequent (ca. 70%). An extended lymphadenectomy, therefore, must be performed in all cases of MEN-1-associated gastrinoma. Following these rules, young adults with advanced disease without disseminated distant metastases, who underwent surgical resection, showed comparable 15-year-survival rates (89–100%) to those with limited disease or without an identifiable tumor (Norton et al. 2001). Hypergastrinemia, however, persists in most cases.

Debulking and metastasectomy can diminish the associated endocrine syndrome and might therefore be appropriate (Shorter et al. 2002). Also, antihormonal pharmacologic therapy (for example, cimetidine in the ulcer-producing Zollinger–Ellison syndrome) has to be considered in these cases (Shorter et al. 2002). The role of chemotherapy and radiotherapy, though, is not clear.

35.5.2.6 Prognosis

In childhood, insulinomas usually show a benign biological behavior; therefore, the prognosis is very good. While 90% of insulinomas are benign, this is the case for only 40% of gastrinomas and 20–30% of glucagonomas (Grosfeld et al. 1990). Large tumors might have metastasized at the time of diagnosis, and metastases may also occur many years after diagnosis (Buetow et al. 1995). As the tumor is slow-growing, these patients might show long survival, which is 20–30% in cases of sporadic gastrinoma (Norton et al. 2004).

35.5.2.7 Other Rare Malignant Pancreatic Tumors

The acinar cell carcinoma probably grows less aggressivly in childhood than in adults (Klimstra et al. 1992; Shorter et al. 2002). The prognosis of the rare pediatric ductal adenocarcinoma is as bad as that in the adult age group (Ivy et al. 1990). Of utmost importance is the complete surgical resection. The impact of chemo- and radiotherapy is not clear (Shorter et al. 2002). The inflammatory myofibroblastic tumor (IMT) has a high tendency for local recurrence. A radical surgical resection, therefore, is of vital importance (Mizukami et al. 2006). Successful treatment using steroids has been described in single cases (Dagash et al. 2009).

35.5.2.8 Benign Tumors

The mucinous cystic adenoma is a benign tumor with the potential of malignant transformation and must be totally resected (Grosfeld et al. 1990). For hemangioma, there is an anecdotal report about a spontaneous regres-

sion after the biopsy (England et al. 2006). Teratoma must be totally resected. A circumscribed fibrotic focus associated with pediatric pancreatitis may mimic a neoplastic process (Adsay et al. 2004). This is one more reason why a mutilating resection should not be performed without knowing the final histological diagnosis.

Pancreatic pseudocysts have a high spontaneous healing rate. Initially, therefore, a wait-and-see policy is indicated. If the size does not decrease and symptoms persist, however, a drainage is necessary. This can be achieved by stent insertion directly into the cyst either percutaneously under sonograpic or CT control imaging (Cannon et al. 2009) or endoscopically via ERCP or through the gastric wall (Sharma et al. and Maharshi 2008). If this fails, an open or laparoscopic cystogastrostomy or cystojejunostomy can be performed (Seitz et al. 2006; Yoder et al. 2009). A cystic pancreatic tumor, however, must be excluded before the drainage (Cannon et al. 2009). If the history or the diagnostic findings are equivocal, there is the rule: better resect a cyst than drain a tumor!

35.5.2.9 Focal Congenital Hyperinsulinism

If the existence and location of a focal congenital hyperinsulinism have been confirmed by ^{18}F-DOPA-PET-CT, surgical resection is indicated. Initially, three small biopsies are taken from unaffected areas and examined as frozen sections to exclude diffuse congenital hyperinsulinism. Then, the focal lesion is excised by atypical excision under frozen section monitoring. If the lesion is located in the pancreatic tail, a left resection is indicated which can be done by laparoscopy. Care is taken to preserve as much pancreatic tissue as possible. The excision is finished if all resection margins of the remaining pancreas are clear. If the pancreatic duct is involved, it must be drained by a Roux-en-Y pancreaticojejunostomy (Barthlen et al. 2008).

35.5.2.10 Laparoscopy

There are numerous reports with reasonable patient numbers about laparoscopic pancreatic resections in benign and malignant disease (Palanivelu et al. 2007). In a study including 103 patients, the conversion rate was only 7% (Fernandez-Esparrach et al. 2007). For solid malignant tumors in childhood, however, these favorable results have not been reproducible (Warmann et al. 2003). The development of metastasis on the trocar sites seems to be quite rare. But even highly experienced centers report about high conversion rates in abdominal tumors (up to 42%) because a satisfying overview cannot be achieved (Metzelder et al. 2007). As outlined before, therefore, the laparoscopic approach for pediatric tumors in the pancreatic head and corpus is not recommended, neither for the biopsy (Fais et al. 2009) nor for the resection with curative intention (Spurbeck et al. 2004). An exception are small, delimited tumors in the pancreatic body or tail, which can be removed by pancreatic tail resection (Sokolov et al. 2009). Possible complications of pancreatic surgery are shown in table (Table 35.6). They are rare.

Table 35.6 Possible complications of pancreatic surgery (Adham et al. 2008)

Complications	
Postoperative bleeding	From the remaining pancreas, small vessels to the splenic vein, bleeding from the splenic vein, portal vein, superior mesenteric vein CAVE! Dangerous are arrosion bleedings after leaking of the suture line or septic complications
Thrombosis or ischemia	Of the splenic artery, splenic vein, portal vein, mesenterial vessels, choledochal duct (after close preparation with stricture)
Loss of the spleen	Due to bleeding or thrombosis with risk of overwhelming post-splenectomy infection (OPSI)
Insufficiency	Stump insufficiency of the pancreas after tail resection, insufficiency of the suture line of a pancreatojejunostomy with secretion of digestive juices, abscess, pseudocyst

35.6 Summary and Conclusions

In case of unspecific pain or a palpable mass in the upper abdomen, a pancreatic tumor should be considered, especially in adolescent females. Ultrasound examination in combination with MRT/CT is mandatory. Because imaging alone is not able to assure histological diagnosis, the tumor should be exposed by an open approach, and the possibility of a primary complete resection without extensive surgery should be evaluated. Laparoscopy is indicated in tumors confined to the pancreatic body and tail, which can be resected without touching the tumor itself. If a complete resection does not seem feasible, biopsy should be performed only. Extensive resections of the pancreas and adjacent organs in childhood are justified

only if they are beneficial for the child in knowledge of the histopathology and the staging. The surgical resection of local recurrences and metastases in childhood is always justified, even multiple times. The role of chemo- and radiotherapy currently is hard to define because only single-case reports have been published.

Endocrine tumors are characterized by their hormone profile, imaging, and scintigraphy. Insulinomas must be treated by surgery, whereas the cure rate of gastrinomas by surgery alone is very low, especially in MEN 1 patients.

Children with pancreatic tumors show generally better prognosis than adults, mainly because of a different histologic pattern of the tumors occurring in that age group, but even in the few cases of pediatric pancreatic carcinomas, better results have been observed. Underlying reasons for a different prognosis, e.g., differences in biology and/or genetic makeup over age groups, are still to be investigated.

References

Abraham SC, Wu TT et al (2001) Distinctive molecular genetic alterations in sporadic and familial adenomatous polyposis-associated pancreatoblastomas: frequent alterations in the APC/beta-catenin pathway and chromosome 11p. Am J Pathol 159(5):1619–1627

Abraham SC, Wu TT et al (2002) Genetic and immunohistochemical analysis of pancreatic acinar cell carcinoma: frequent allelic loss on chromosome 11p and alterations in the APC/beta-catenin pathway. Am J Pathol 160(3):953–962

Adham M, Giunippero A et al (2008) Central pancreatectomy: single-center experience of 50 cases. Arch Surg 143(2):175–180; discussion 180–171

Adsay NV, Basturk O et al (2004) Pancreatic pseudotumors: non-neoplastic solid lesions of the pancreas that clinically mimic pancreas cancer. Semin Diagn Pathol 21(4): 260–267

AJCC (2006) Exocrine pancreas. In: Greene FL, Compton CC, Fritz AG, Shah JP, Winchester DP (eds) AJCC cancer staging atlas, 6th edn. Springer, New York, pp 155–163

Anlauf M, Sipos B et al (2005) Tumors of the endocrine pancreas. Pathologe 26(1):46–51

Anlauf M, Wieben D et al (2005) Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis: diagnostic criteria, incidence, and characterization of beta-cell changes. Am J Surg Pathol. 29(4):524–533

Antonello D, Gobbo S et al (2009) Update on the molecular pathogenesis of pancreatic tumors other than common ductal adenocarcinoma. Pancreatology 9(1–2):25–33

Barthlen W, Blankenstein O et al (2008) Evaluation of [18F] fluoro-L-DOPA positron emission tomography-computed tomography for surgery in focal congenital hyperinsulinism. J Clin Endocrinol Metab 93(3):869–875

Bartsch DK, Kersting M et al (2000) Low frequency of p16(INK4a) alterations in insulinomas. Digestion 62(2–3):171–177

Bosman F.T., Carneiro F., Hruban R.H., Theise N.D. (Eds.): WHO Classification of Tumours of the Digestive System. Lyon 2010

Brandi ML, Gagel RF et al (2001) Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 86(12):5658-5671. Review

Brennan MF, Kattan MW et al (2004) Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. Ann Surg 240(2):293–298

Bien E, Godzinski J, Dall'igna P et al (2011). Pancreatoblastoma: A report from the European cooperative study group for paediatric rare tumours (EXPeRT). Eur J Cancer Oct; 47(15):2347–52. Epub 2011 Jun 21

Buetow PC, Parrino TV et al (1995) Islet cell tumors of the pancreas: pathologic-imaging correlation among size, necrosis and cysts, calcification, malignant behavior, and functional status. AJR Am J Roentgenol 165(5):1175–1179

Campanile M, Nicolas A et al (2011) Frantz's tumor: is mutilating surgery always justified in young patients? Surg Oncol 20(2):121–125

Cannon JW, Callery MP et al (2009) Diagnosis and management of pancreatic pseudocysts: what is the evidence? J Am Coll Surg 209(3):385–393

Casanova M, Collini P et al (2003) Solid-pseudopapillary tumor of the pancreas (Frantz tumor) in children. Med Pediatr Oncol 41(1):74–76

Chu QD, Hill HC et al (2002) Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. Ann Surg Oncol 9(9):855–862

Chun Y, Kim W et al (1997) Pancreatoblastoma. J Pediatr Surg 32(11):1612–1615

Chung EM, Travis MD et al (2006) Pancreatic tumors in children: radiologic-pathologic correlation. Radiographics 26(4): 1211–1238

Correa-Gallego C, Ferrone CR et al (2010) Incidental pancreatic cysts: do we really know what we are watching? Pancreatology 10(2–3):144–150

Dagash H, Koh C et al (2009) Inflammatory myofibroblastic tumor of the pancreas: a case report of 2 pediatric cases–steroids or surgery? J Pediatr Surg 44(9):1839–1841

Dall'igna P, Cecchetto G et al (2010) Pancreatic tumors in children and adolescents: the Italian TREP project experience. Pediatr Blood Cancer 54(5):675–680

Defachelles AS, Martin De Lassalle E et al (2001) Pancreatoblastoma in childhood: clinical course and therapeutic management of seven patients. Med Pediatr Oncol 37(1):47–52

de Lonlay P, Simon-Carre A et al (2006). Congenital hyperinsulinism: pancreatic [18F]fluoro-L-dihydroxyphenylalanine (DOPA) positron emission tomography and immunohistochemistry study of DOPA decarboxylase and insulin secretion. J Clin Endocrinol Metab 91(3):933–940

Dhebri AR, Connor S et al (2004) Diagnosis, treatment and outcome of pancreatoblastoma. Pancreatology 4(5):441–451; discussion 452–443

Donow C, Pipeleers-Marichal M et al (1990) The pathology of insulinoma and gastrinoma. The location, size, multicentricity, association with multiple endocrine type-I neoplasms and malignancy. Dtsch Med Wochenschr 115(37): 1386–1391

England RJ, Woodley H et al (2006) Pediatric pancreatic hemangioma: a case report and literature review. Jop 7(5):496–501
Fais PO, Carricaburu E et al (2009) Is laparoscopic management suitable for solid pseudo-papillary tumors of the pancreas? Pediatr Surg Int 25(7):617–621
Fernandez-Esparrach G, Gines A et al (2007) Comparison of endoscopic ultrasonography and magnetic resonance cholangiopancreatography in the diagnosis of pancreatobiliary diseases: a prospective study. Am J Gastroenterol 102(8):1632–1639
Field JB (1993) Insulinoma. In: Mazzaferri EL, Samaan NA (eds) Endocrine tumors. Blackwell Scientific Publications, Boston, pp 497–530
Fisher JC, Kuenzler KA et al (2007) Central pancreatectomy with pancreaticogastrostomy in children. J Pediatr Surg 42(4):740–746
Fried P, Cooper J et al (1985) A role for radiotherapy in the treatment of solid and papillary neoplasms of the pancreas. Cancer 56(12):2783–2785
Fukushima N, Fukayama M (2007) Mucinous cystic neoplasms of the pancreas: pathology and molecular genetics. J Hepatobiliary Pancreat Surg 14(3):238–242
Garcea G, Ong SL et al (2008) Cystic lesions of the pancreas. A diagnostic and management dilemma. Pancreatology 8(3): 236–251
Goh BK, Tan YM et al (2007) Solid pseudopapillary neoplasms of the pancreas: an updated experience. J Surg Oncol 95(8): 640–644
Gonzalez-Campora R, Rios Martin JJ et al (1995) Papillary cystic neoplasm of the pancreas with liver metastasis coexisting with thyroid papillary carcinoma. Arch Pathol Lab Med 119(3):268–273
Griffin BR, Wisbeck WM et al (1987) Radiotherapy for locally recurrent infantile pancreatic carcinoma (pancreatoblastoma). Cancer 60(8):1734–1736
Grosfeld JL, Vane DW et al (1990) Pancreatic tumors in childhood: analysis of 13 cases. J Pediatr Surg 25(10): 1057–1062
Gupta AK, Mitra DK et al (2000) Sonography and CT of pancreatoblastoma in children. AJR Am J Roentgenol 174(6): 1639–1641
Hamilton S.R., Aaltonen L.A. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. IARC Press. Lyon 2000
Herrmann KA, Helmberger T et al (2008) Solid pseudopapillary pancreas tumors–often neglected. Radiologe 48(8):764–769
Hochwald SN, Zee S et al (2002) Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. J Clin Oncol 20(11):2633–2642
Imamura A, Nakagawa A et al (1998) Pancreatoblastoma in an adolescent girl: case report and review of 26 Japanese cases. Eur J Surg 164(4):309–312
Ivy EJ, Sarr MG et al (1990) Nonendocrine cancer of the pancreas in patients under age forty years. Surgery 108(3):481–487
Jaksic T, Yaman M et al (1992) A 20-year review of pediatric pancreatic tumors. J Pediatr Surg 27(10):1315–1317
Jeng LB, Chen MF et al (1993) Solid and papillary neoplasm of the pancreas. Emphasis on surgical treatment. Arch Surg 128(4):433–436
Kaufman SL, Reddick RL et al (1986) Papillary cystic neoplasm of the pancreas: a curable pancreatic tumor. World J Surg 10(5):851–859
Kauhanen S, Seppanen M et al (2007) Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography as a tool to localize an insulinoma or beta-cell hyperplasia in adult patients. J Clin Endocrinol Metab 92(4):1237–1244
Kela M, Singh S, Lahoti B (2008) Immature cystic teratoma of head of pancreas. J Indian Assoc Pediatr Surg. 13(2):85–87
Kerr NJ, Chun YH et al (2002) Pancreatoblastoma is associated with chromosome 11p loss of heterozygosity and IGF2 overexpression. Med Pediatr Oncol 39(1):52–54
Klimstra DS, Heffess CS et al (1992) Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. Am J Surg Pathol 16(9):815–837
Klimstra DS, Wenig BM et al (1995) Pancreatoblastoma. A clinicopathologic study and review of the literature. Am J Surg Pathol 19(12):1371–1389
Klimstra DS, Wenig BM et al (2000) Solid-pseudopapillary tumor of the pancreas: a typically cystic carcinoma of low malignant potential. Semin Diagn Pathol 17(1):66–80
Kloppel G, Solcia E et al (1996) Histological typing of tumors of the exocrine pancreas. WHO international histological classification of tumors, 2nd edn. Springer, Berlin/Heidelberg/New York
Kohda E, Iseki M et al (2000) Pancreatoblastoma. Three original cases and review of the literature. Acta Radiol 41(4): 334–337
Kosmahl M, Seada LS et al (2000) Solid-pseudopapillary tumor of the pancreas: its origin revisited. Virchows Arch 436(5):473–480
Kosmahl M, Pauser U et al (2004) Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch 445(2):168–178
La Rosa S, Sessa F et al (1996) Prognostic criteria in nonfunctioning pancreatic endocrine tumours. Virchows Arch 429(6):323–333
Lack EE (1989) Primary tumors of the exocrine pancreas. Classification, overview, and recent contributions by immunohistochemistry and electron microscopy. Am J Surg Pathol 13 Suppl 1:66–88
Lack EE, Cassady JR et al (1983) Tumors of the exocrine pancreas in children and adolescents. A clinical and pathologic study of eight cases. Am J Surg Pathol 7(4):319–327
Lam KY, Lo CY et al (1999) Pancreatic solid-cystic-papillary tumor: clinicopathologic features in eight patients from Hong Kong and review of the literature. World J Surg 23(10):1045–1050
Lodish MB, Powell AC et al (2008) Insulinoma and gastrinoma syndromes from a single intrapancreatic neuroendocrine tumor. J Clin Endocrinol Metab 93(4):1123–1128
Luttges J, Stigge C et al (2004) Rare ductal adenocarcinoma of the pancreas in patients younger than age 40 years. Cancer 100(1):173–182
Machado MC, da Cunha JE et al (2001) Insulinoma: diagnostic strategies and surgical treatment. A 22-year experience. Hepatogastroenterology 48(39):854–858
Maffuz A, Bustamante Fde T et al (2005) Preoperative gemcitabine for unresectable, solid pseudopapillary tumour of the pancreas. Lancet Oncol 6(3):185–186
Mao C, Guvendi M et al (1995) Papillary cystic and solid tumors of the pancreas: a pancreatic embryonic tumor? Studies of three cases and cumulative review of the world's literature. Surgery 118(5):821–828

Martin RC, Klimstra DS et al (2002) Solid-pseudopapillary tumor of the pancreas: a surgical enigma? Ann Surg Oncol 9(1):35–40

Matsunou H, Konishi F (1990) Papillary-cystic neoplasm of the pancreas. A clinicopathologic study concerning the tumor aging and malignancy of nine cases. Cancer 65(2): 283–291

Mergo PJ, Helmberger TK et al (1997) Pancreatic neoplasms: MR imaging and pathologic correlation. Radiographics 17(2):281–301

Mester M, Trajber et al (1990) Cystic teratomas of the pancreas. Arch Surg. 125(9):1215–1258

Metzelder ML, Kuebler JF et al (2007) Role of diagnostic and ablative minimally invasive surgery for pediatric malignancies. Cancer 109(11):2343–2348

Mizukami H, Yajima N et al (2006) Pancreatic malignant fibrous histiocytoma, inflammatory myofibroblastic tumor, and inflammatory pseudotumor related to autoimmune pancreatitis: characterization and differential diagnosis. Virchows Arch 448(5):552–560

Montemarano H, Lonergan GJ et al (2000) Pancreatoblastoma: imaging findings in 10 patients and review of the literature. Radiology 214(2):476–482

Murakami T, Ueki K et al (1996) Pancreatoblastoma: case report and review of treatment in the literature. Med Pediatr Oncol 27(3):193–197

Nadler EP, Novikov A et al (2002) The use of endoscopic ultrasound in the diagnosis of solid pseudopapillary tumors of the pancreas in children. J Pediatr Surg 37(9):1370–1373

Nishihara K, Nagoshi M et al (1993a) Papillary cystic tumors of the pancreas. Assessment of their malignant potential. Cancer 71(1):82–92

Nishihara K, Tsuneyoshi M et al (1993b) Papillary cystic tumor of the pancreas. Is it a hormone-dependent neoplasm? Pathol Res Pract 189(5):521–526

Norton JA, Alexander HR et al (2001) Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 234(4):495–505; discussion 505–496

Norton JA, Alexander HR et al (2004) Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger-Ellison syndrome? Ann Surg 239(5):617–625; discussion 626

Ogawa T, Isaji S et al (1993) A case of radical resection for solid cystic tumor of the pancreas with widespread metastases in the liver and greater omentum. Am J Gastroenterol 88(9): 1436–1439

Ogawa B, Okinaga K et al (2000) Pancreatoblastoma treated by delayed operation after effective chemotherapy. J Pediatr Surg 35(11):1663–1665

Orlefors H, Sundin A et al (2005) Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. J Clin Endocrinol Metab 90(6): 3392–3400

Palanivelu C, Jani K et al (2007) Laparoscopic pancreaticoduodenectomy: technique and outcomes. J Am Coll Surg 205(2):222–230

Panieri E, Krige JE et al (1998) Operative management of papillary cystic neoplasms of the pancreas. J Am Coll Surg 186(3):319–324

Papavramidis T, Papavramidis S (2005) Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. J Am Coll Surg 200(6):965–972

Pappo AS, Furman WL (2006) Management of infrequent cancers in childhood. In: Pizzo PA, Poplack DC (eds) Principles and practice of pediatric oncology, 5th edn. Lippincott Williams & Wilkins, Philadelphia, pp 1180–1182

Perez EA, Gutierrez JC et al (2009) Malignant pancreatic tumors: incidence and outcome in 58 pediatric patients. J Pediatr Surg 44(1):197–203

Perilongo G, Brown J et al (2000) Hepatoblastoma presenting with lung metastases: treatment results of the first cooperative, prospective study of the International Society of Paediatric Oncology on childhood liver tumors. Cancer 89(8):1845–1853

Rebhandl W, Felberbauer FX et al (2001) Solid-pseudopapillary tumor of the pancreas (Frantz tumor) in children: report of four cases and review of the literature. J Surg Oncol 76(4):289–296

Rebours V, Boutron-Ruault MC et al (2009) The natural history of hereditary pancreatitis: a national series. Gut 58(1):97–103

Saif MW (2007) Pancreatoblastoma. Jop 8(1):55–63

Saiura A, Umekita N et al (2000) Successful surgical resection of solid cystic tumor of the pancreas with multiple liver metastases and a tumor thrombus in the portal vein. Hepatogastroenterology 47(33):887–889

Sclafani LM, Reuter VE et al (1991) The malignant nature of papillary and cystic neoplasm of the pancreas. Cancer 68(1):153–158

Seitz G, Warmann SW et al (2006) Laparoscopic cystojejunostomy as a treatment option for pancreatic pseudocysts in children–a case report. J Pediatr Surg 41(12):e33–e35

Service FJ, McMahon MM et al (1991) Functioning insulinoma–incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc 66(7):711–719

Sharma SS, Maharshi S (2008) Endoscopic management of pancreatic pseudocyst in children-a long-term follow-up. J Pediatr Surg 43(9):1636–1639

Shorter NA, Glick RD et al (2002) Malignant pancreatic tumors in childhood and adolescence: the Memorial Sloan-Kettering experience, 1967 to present. J Pediatr Surg 37(6):887–892

Singhal D, Kakodkar R et al (2006) Issues in management of pancreatic pseudocysts. Jop 7(5):502–507

Sipos B, Kloppel G (2005) Acinar cell carcinomas and pancreatoblastomas: related but not the same. Pathologe 26(1): 37–40

Snajdauf J, Rygl M et al (2009) Duodenum-sparing technique of head resection in solid pseudopapillary tumor of the pancreas in children. Eur J Pediatr Surg 19(6):354–357

Sokolov YY, Stonogin SV et al (2009) Laparoscopic pancreatic resections for solid pseudopapillary tumor in children. Eur J Pediatr Surg 19(6):399–401

Solcia E, Klöppel G et al (2000) Histological typing of endocrine tumours. WHO international histological classification of tumours, 2nd edn. Springer, Berlin

Sperti C, Berselli M et al (2008) Aggressive behaviour of solid-pseudopapillary tumor of the pancreas in adults: a case report and review of the literature. World J Gastroenterol 14(6): 960–965

Spurbeck WW, Davidoff AM et al (2004) Minimally invasive surgery in pediatric cancer patients. Ann Surg Oncol 11(3): 340–343

Strauss JF, Hirsch VJ et al (1993) Resection of a solid and papillary epithelial neoplasm of the pancreas following treatment with cis-platinum and 5-fluorouracil: a case report. Med Pediatr Oncol 21(5):365–367

Sugai M, Kimura N et al (2006) A case of pancreatoblastoma prenatally diagnosed as intraperitoneal cyst. Pediatr Surg Int 22(10):845–847

Tessonnier L, Sebag F et al (2010) Limited value of 18F-F-DOPA PET to localize pancreatic insulin-secreting tumors in adults with hyperinsulinemic hypoglycemia. J Clin Endocrinol Metab 95(1):303–307

Tipton SG, Smyrk TC et al (2006) Malignant potential of solid pseudopapillary neoplasm of the pancreas. Br J Surg 93(6):733–737

Todani T, Shimada K et al (1988) Frantz's tumor: a papillary and cystic tumor of the pancreas in girls. J Pediatr Surg 23(2): 116–121

Vannier JP, Flamant F et al (1991) Pancreatoblastoma: response to chemotherapy. Med Pediatr Oncol 19(3):187–191

Vossen S, Goretzki PE et al (1998) Therapeutic management of rare malignant pancreatic tumors in children. World J Surg 22(8):879–882

Wang KS, Albanese C et al (1998) Papillary cystic neoplasm of the pancreas: a report of three pediatric cases and literature review. J Pediatr Surg 33(6):842–845

Warmann S, Fuchs J et al (2003) A prospective study of minimally invasive techniques in pediatric surgical oncology: preliminary report. Med Pediatr Oncol 40(3):155–157

Wunsch LP, Flemming P et al (1997) Diagnosis and treatment of papillary cystic tumor of the pancreas in children. Eur J Pediatr Surg 7(1):45–47

Yeung MJ, Pasieka JL (2009) Gastrinomas: a historical perspective. J Surg Oncol 100(5):425–433

Yoder SM, Rothenberg S et al (2009) Laparoscopic treatment of pancreatic pseudocysts in children. J Laparoendosc Adv Surg Tech A 19 Suppl 1:S37–S40

Yu DC, Kozakewich HP et al (2009) Childhood pancreatic tumors: a single institution experience. J Pediatr Surg 44(12):2267–2272

Zhou H, Cheng W et al (2001) Solid-cystic papillary tumor of the pancreas in children. Pediatr Surg Int 17(8):614–620

Zollinger RM (1987) Gastrinoma: the Zollinger-Ellison syndrome. Semin Oncol 14(3):247–252

Liver Tumors

36

Childhood Liver Cancers

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36.1 Genetics and Etiology

The underlying etiology of most pediatric liver tumors remains largely unknown; however, several genetic syndromes have been observed to be associated with hepatoblastoma. Beckwith-Wiedemann syndrome (BWS) is an overgrowth syndrome linked to chromosome 11p and is present in approximately 2% of patients with hepatoblastoma. Patients with BWS are at increased risk for the development of several cancers including hepatoblastoma, Wilms' tumor, neuroblastoma, and adrenocortical carcinoma. A BWS registry has observed that hepatoblastoma is the most common tumor that occurs in BWS and that the risk for the development of hepatoblastoma in children with BWS is over 2,000-fold higher than normal (DeBaun and Tucker 1998). Accordingly, it is recommended that BWS children be routinely screened with abdominal ultrasounds and serum alpha-fetoprotein levels every 3 months during the first decade of life to facilitate early detection (Clericuzio et al. 2003).

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder in which colonic polyp growth develops during adolescence and, without medical intervention, leads to colon cancer. FAP is also associated with a high risk of hepatoblastoma (Clericuzio et al. 2003). Mutations in the adenomatous polyposis coli (APC) gene on chromosome 5q can be detected in children with hepatoblastoma who have a family history of early occurrence of colon cancer. While it is unclear what the risk of this cancer predisposition is in children with hepatoblastoma without a history of FAP, it has

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been recommended that all children with hepatoblastoma should be evaluated for APC mutations and that asymptomatic children from FAP kindreds be screened to detect presence of the mutation. If APC mutations are observed, then accordingly periodic screening for hepatoblastoma is warranted (Hirschman et al. 2005).

Several other syndromes have been reported in association with hepatoblastoma including Simpson-Golabie-Behmel syndrome and trisomy of chromosome 8. Other rare genetic disorders with underlying liver disease, including progressive familial intrahepatic cholestasis, Alagille syndrome, hereditary tyrosinemia, and glycogen storage disease, are also linked to the development of hepatocellular carcinoma. Hepatocellular carcinoma has been described to occur in children with Fanconi's anemia who receive treatment with androgenic steroids.

The strongest risk factor associated with the development of hepatocellular carcinoma is hepatitis B or C infection. In endemic areas of Southeast Asia, where hepatitis B and C infection rates are high, hepatocellular carcinoma is associated with the preponderance of malignant pediatric liver cancers (Chang et al. 1997). The utilization of hepatitis B vaccine has significantly diminished the incidence of hepatocellular carcinoma. In children, hepatocellular carcinoma can develop without any previous viral infections. In children, hepatocellualr carcinoma can develop without any previous viral infections and tumor development may be associated with congential hepatic disorders (Czauderna 2002; Czauderna et al. 2002).

Epidemiologic studies have observed an increased risk of hepatoblastoma in children with fetal alcohol syndrome, with maternal use of oral contraceptives, and in parents who smoke. Surveys of exposures related to parental occupations in children with hepatoblastoma have shown a higher incidence of exposure to metals, welding, petroleum products, paints, and pigments (Buckley et al. 1989).

An increased risk of hepatoblastoma has been observed in children born prematurely, and this risk is inversely related to birth weight (Spector et al. 2004). The improved survival of low birth weight infants over recent decades may be an important contributing factor to the increased incidence of liver tumors observed over the past 20 years (Spector et al. 2004). Studies are ongoing to ascertain the etiology behind this phenomenon, which may be related to environmental exposures within newborn nurseries, enhanced sensitivity of the premature liver, interference in prenatal developmental pathways, or a multifactorial combination of such events.

36.2 Pathology and Cellular Classification

Hepatoblastoma is the most common malignant liver tumor in children. Hepatoblastoma arises from hepatic precursors and may present with varying histology. Histology, typical for hepatoblastoma, is shown in Fig. 36.1. The tumors often contain a mixture of epithelial hepatocytic precursors or pure hepatic embryonal cells. Two important variants may have clinical relevance: pure fetal histology (throughout the entire tumor) and foci of small undifferentiated cells. In the United States, the treatment strategy has favored surgical resection at diagnosis, if surgeon is confident that complete resection can be obtained. Patients whose tumors have pure fetal histology and undergo complete resection have a better prognosis (Ortega et al. 2000; Malogolowkin 2011). Small cell undifferentiated hepatoblastoma is uncommon and is usually seen under 1 year of age (Rowland 2002; Trobaugh-Lotrario et al. 2009). The AFP is often low. Histologically, small cell undifferentiated hepatoblastoma presents with a diffuse population of small cells with scant cytoplasm.

36.2.1 Hepatocellular Carcinoma

Hepatocellular carcinoma can be seen in children, and the histology has predominately epithelial features (Fig. 36.2). They may form sinusoidal-like vascular channels with trabeculations. A distinct variant, fibrolamellar carcinoma has been described in older children and young adults (Katzenstein et al. 2003b). Transitional liver cell tumors have been recently identified in older children and adolescents (Prokurat et al. 2002). They usually present as a solitary large mass (often in right lobe of liver). Cells are described as intermediate between hepatoblasts and mature hepatocytes.

36.2.2 Sarcomas and Undifferentiated Embryonal Sarcoma of the Liver

Various sarcomas have been identified in liver including biliary rhabdomyosarcoma, angiosarcomas, and rhabdoid tumors of the liver. Undifferentiated embryonal sarcoma of the liver is a unique entity. Histologically,

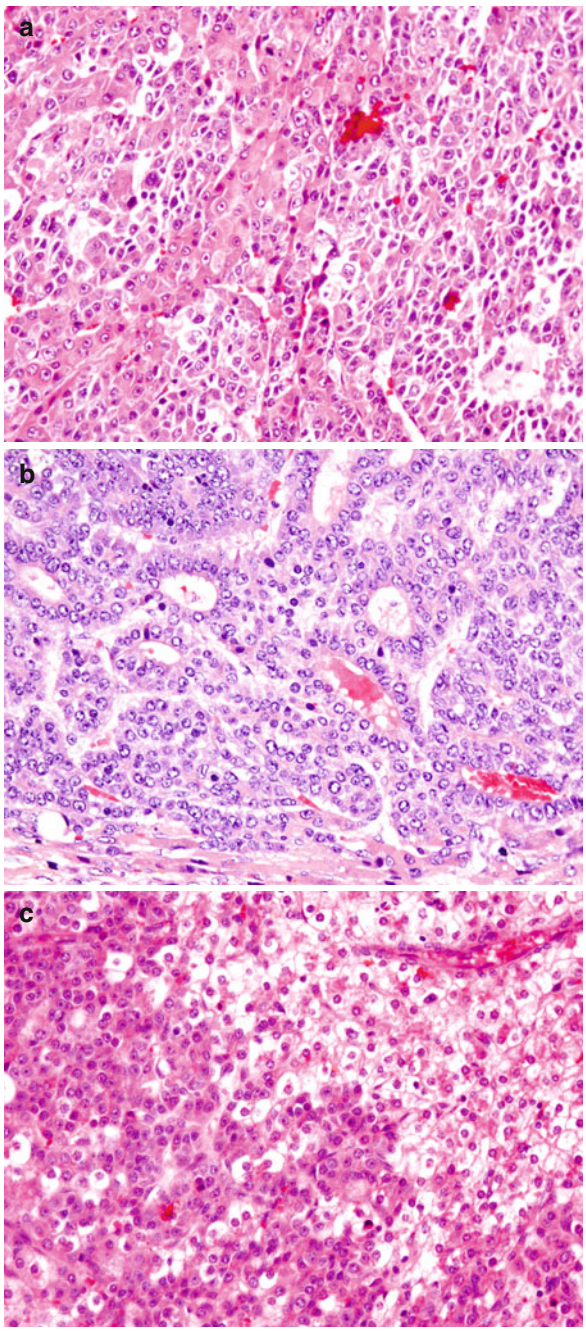

Fig. 36.1 (**a**) Hepatoblastoma, epithelial mixed type (embryonal and fetal). (**b**) Hepatoblastoma, pure embryonal type. (**c**) Hepatoblastoma, pure fetal type showing light and dark pattern

intracellular hyaline globules and marked anaplasia are seen in a mesenchymal background. Infantile choriocarcinoma of the liver are identified by closely packed cells with clear cytoplasm and multinucleated syncytia formation (see chapter 39).

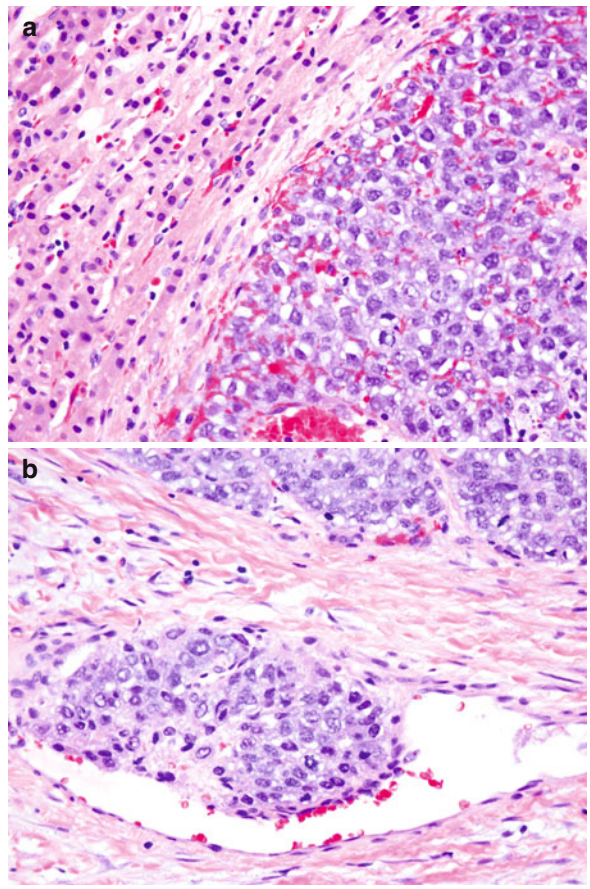

Fig. 36.2 (**a**) Hepatocellular carcinoma, showing normal liver on left and tumor on right. (**b**) Hepatocellular carcinoma, showing angiolymphatic invasion

36.3 Clinical Diagnosis

Liver tumors in children have a wide constellation of presenting symptoms but do not have a pathognomonic presentation. Most patients present with an asymptomatic lesion or with an incidentally detected right upper quadrant mass in patients with other complaints such as abdominal pain, nausea, vomiting, weight loss, and fever. Systemic symptoms may indicate tumor rupture. At diagnosis, most children will not have any evidence of underlying liver disease such as ascites, jaundice, or abnormal tests of liver function. Hepatoblastoma is high in the differential diagnosis of patients with predisposing conditions such as a history of prematurity, hemihypertrophy, BWS, a family history of early colon cancers, or precocious puberty. Hepatocellular carcinoma usually occurs in an otherwise asymptomatic

patient but may arise in patients with antecedent conditions such as Hepatitis B or C infection, cirrhosis, galactosemia, tyrosinemia, α-1 antitrypsin deficiency, or glycogen storage disease. The rarest of malignant pediatric liver tumors, sarcomas and rhabdoid tumors, are usually not considered as a diagnosis until review of tissue biopsies or in patients with characteristic radiographic findings. Metastatic involvement of the liver from neuroblastoma, Wilms' tumor, sarcomas, lymphoma, and leukemia are more common than most primary liver malignancies and may be identifiable within the characteristic presentations of such oncologic processes.

Benign tumors are also often asymptomatic at diagnosis. Hemangiomas and hemangioendotheliomas usually occur early in life and may present as part of the Kasabach-Merritt syndrome with high output cardiac failure or consumptive coagulopathy. In adolescent girls with a history of using oral contraceptive, adenomas should be considered.

36.3.1 Diagnosis and Evaluation

Serum alpha-fetoprotein (AFP) is an extremely helpful tumor marker in the diagnosis and follow-up of liver tumor patients and should be evaluated in all patients at presentation. AFP elevation is usually a sign of malignant disease. Tests for AFP can often be falsely low in what is referred to as the "hook effect" if the assay is not sensitive enough to detect a very high level (Jassam et al. 2006). Normal AFP levels in suspected malignancies should have serial dilutions performed to ascertain whether or not the hook effect is present. In the first year of life, and especially in the first 6 months, interpretation of AFP levels can be difficult and must be evaluated within the context of age appropriate normal values (Wu et al. 1981; Blohm et al. 1998). AFP levels are elevated at diagnosis in the majority of hepatoblastoma patients but in only about half of hepatocellular carcinoma patients. A normal AFP level should question the diagnosis of hepatoblastoma, but the AFP can be normal in a very small portion of high-risk hepatoblastoma patients. In addition, a normal AFP is usually found in cases of fibrolamellar hepatocellular carcinoma, undifferentiated sarcomas, rhabdoid tumors, as well as metastatic disease. The decline of the AFP in response to chemotherapy is a useful marker of tumor response. Failure of the AFP level to decline or AFP increases during both therapy and follow-up can signify resistant or recurrent disease. Minimal elevations can be seen following surgery or as a result of tumor necrosis following the initiation of therapy. Recurrent disease as suggested by elevations of AFP should be confirmed by imaging studies. However, it is sometimes difficult to find recurrent lesions when the AFP has just started to increase. In fibrolamellar hepatocellular carcinoma, elevated levels of vitamin B12-binding protein can sometimes be used to monitor disease (Lin et al. 2010).

Thrombocytosis and anemia can sometimes be observed at diagnosis. In most instances, liver function tests are usually normal or minimally elevated, except in the setting of underlying liver disease.

Abdominal ultrasound is typically the first radiologic exam performed in patients with newly identified liver lesions. Computerized tomography (CT) and/or magnetic resonance imaging of the abdomen provide definitive tumor imaging. As the lungs are the primary site of metastatic disease, a CT scan of the chest should be performed preoperatively in all patients suspected of malignancy. Angiographic studies which delineate tumor vascularity and blood supply are often extremely helpful in guiding decisions about tumor resectability. The utility of positron emission tomography (PET) imaging in pediatric liver tumors is not established at this time.

Metastatic disease to sites other than lung is extremely rare but has been described to occur in the bone, bone marrow, and brain. Imaging of these sites should only be considered if the clinical scenario suggests the presence of such disease.

36.4 Tumor Staging

The Children's Oncology Group has used a surgical staging system (Table 36.1). Stage I and II are grossly resected tumors with and without microscopic residual, respectively. The majority of tumors are stage III with gross residual disease but no extrahepatic spread. Stage IV patients have distant metastasis. In contrast, the International Childhood Liver Tumor Strategy Group (SIOPEL) has established the PRETEXT (pretreatment extent of disease) system (Fig. 36.3) which uses the radiologic appearance of the tumor to determine tumor involvement of 4 different sectors and the 8 different Couinaud segments (Aronson et al. 2005). This system guides resectability and is linked to

Table 36.1 Surgical staging of primary tumor at time of initial surgery

Stage I:	Completely resected tumors Note: All stage I tumors require rapid pathology review prior to enrollment.
Stage II:	Grossly resected tumors with evidence of microscopic residual Resected tumors with microscopic positive margins or preoperative (intraoperative) rupture. Note: All stage II tumors require rapid pathology review prior to enrollment.
Stage III:	Unresectable tumors Partially resected tumors with measurable tumor left behind or patients with abdominal lymph node involvement.
Stage IV:	Metastatic disease to lungs, other organs, or sites distant from the abdomen

outcome. However, some initial studies have suggested significant over staging using this system as well as questionable interobserver reliability (Aronson et al. 2005). This system will be useful in allowing international comparison of trial results but still requires further validation for prognostic significance.

36.5 Prognostic Factors

The surgical resectability of the tumor and the absence of metastatic disease are the most important prognostic factors in pediatric liver tumors. The PRETEXT system can predict outcome. More recent evidence has revealed that tumor pathology can also predict outcome. Patients with pure fetal histology hepatoblastoma tumors that

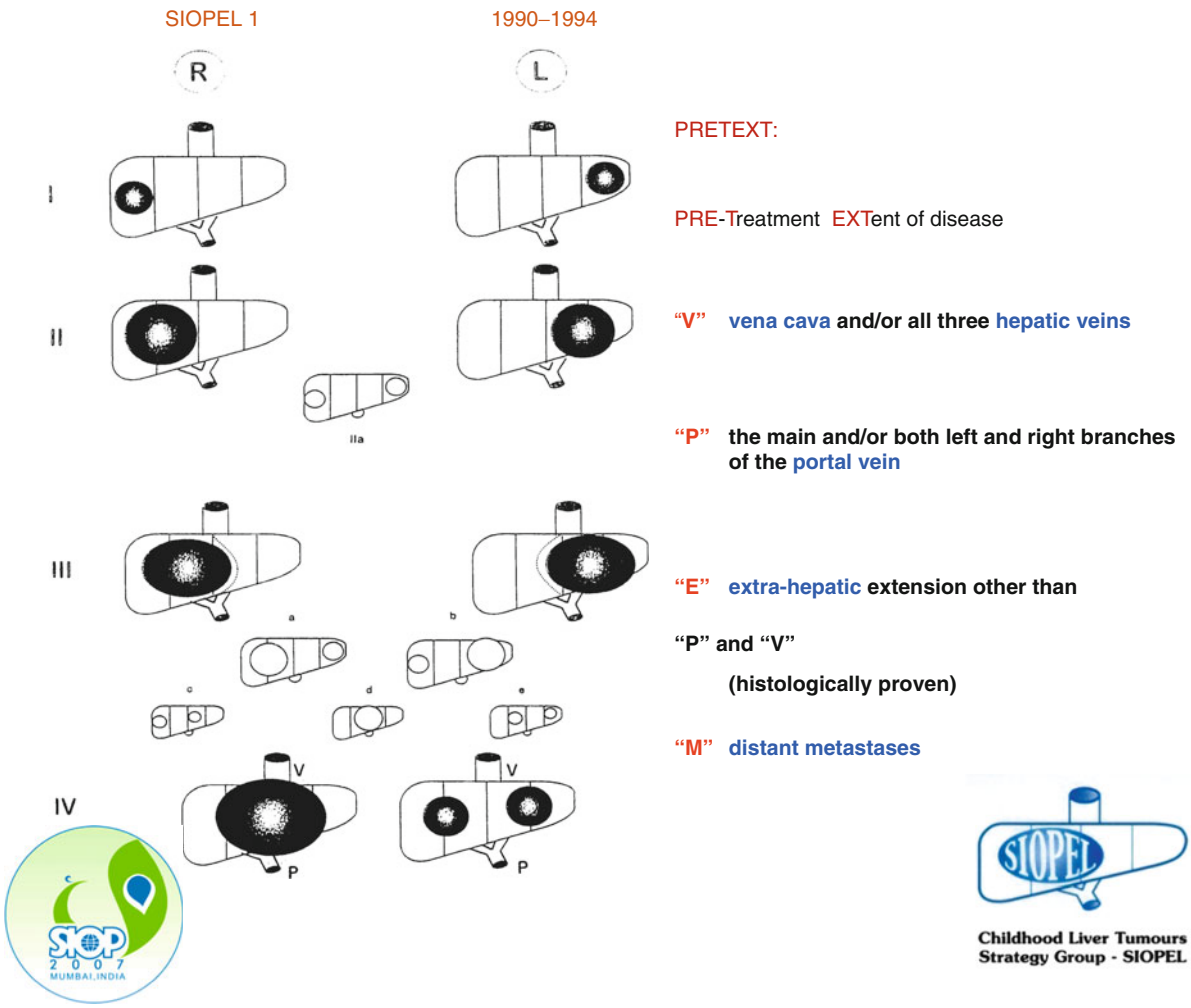

Fig. 36.3 PRETEXT classification of liver tumors

are completely resected at diagnosis have a superb outcome (Malogolowkin 2011), while patients with small cell undifferentiated histology are often associated with a low AFP (<100 ng/ml) and have a dismal outlook (Haas et al. 2001). Patients with fibrolamellar hepatocellular carcinoma subtype, though previously described to be associated with a survival advantage, have a similar overall outcome as other hepatocellular carcinoma patients (Katzenstein et al. 2003b). The decline of AFP levels is another prognostic variable, as patients with hepatoblastoma, who have a >1 log decline over the entire course of therapy, do better (Van Tornout et al. 1997). However, the rate of AFP decline during therapy has not been able to determine patients at increased risk of relapse. Undifferentiated embryonal sarcomas of the liver are considered very aggressive tumors, with poor prognosis. Multimodal therapies may be of some benefit.

36.6 Treatment

Surgical resection is the foundation of curative treatment for both hepatoblastoma and hepatocellular carcinoma. Liver transplantation, as potential curative therapy, is an important alternative for achieving surgical resection (Otte et al. 2004). Extrahepatic disease is a contraindication to liver transplantation, and therefore, strong consideration should be given to the aggressive removal of metastatic foci to make a patient a viable candidate for liver transplant. The scarcity of liver tumors makes it crucial to consider early referral to centers with experience and expertise in performing liver transplantation for any patient who has unresectable disease at diagnosis. Typically, less than half of children with hepatoblastoma and one third of patients with hepatocellular carcinoma have resectable disease at diagnosis. Patients who do not undergo upfront resection usually receive a more prolonged course of chemotherapy treatment with potential for an increased amount of late effects. While hepatoblastoma is considered a surgical disease, the importance and role of surgical resection of metastatic sites remain unclear (Meyers et al. 2007). It requires a prospective study to determine whether there is a difference in outcome for patients who have chemotherapeutic eradication of metastatic disease compared with those who undergo surgical metastasectomy.

Over the last two decades, chemotherapy has been demonstrated to be effective in improving the survival of patients with hepatoblastoma by making tumors surgically resectable. Treatment approaches in North American cooperative group trials have differed somewhat from international treatment regimens. Cisplatin and doxorubicin are considered to be the most effective agents. The combination of cisplatin, 5-flourouracil, and vincristine (C5V) has demonstrated excellent survival in the approximately one third of patients with low-risk disease who are able to undergo resection at diagnosis (Ortega et al. 2000). The role of doxorubicin has been debated but is used in the majority of patients with high-risk disease that is either unresectable or metastatic (Pritchard et al. 2000; Malogolowkin et al. 2008). Carboplatin, ifosfamide, and etoposide have been used in treatment regimens, but there are no single agent data establishing the effectiveness of these drugs (von Schweinitz et al. 1997). Due to the low numbers of cases of pediatric liver tumors, it has been challenging to identify active new compounds in phase I and II trials. Irinotecan is a newer agent which has shown some efficacy and is being studied in current trials (Qayed et al. 2010). Contrastingly, the novel platin compound oxaliplatin had disappointing phase II results against liver tumors (Beaty et al. 2010).

The chemotherapy drugs used for the treatment of hepatoblastoma have also been utilized in combined trials for hepatocellular carcinoma, but with much different results. Patients with resected hepatocellular carcinoma have received chemotherapy post resection with excellent results. It is unclear if these patients were cured with surgery alone or if there was any contributing role for chemotherapy (Katzenstein et al. 2002). This remains a study question for future trials. On the other hand, for patients with unresectable or metastatic disease, chemotherapy is largely ineffective in rendering a tumor resectable or in eliminating metastatic disease. Interferon has been used in adult trials without much success. Sorafenib has shown some efficacy in prolonging survival in adult trials and is now widely considered as standard of care (Abou-Alfa et al. 2010). This agent has been used in pediatric phase I and II studies but has yet to be formally evaluated in a pediatric liver tumor trial. Because of the lack of chemotherapeutic efficacy, earlier consideration should be given to liver transplantation so that tumor does not spread during the administration of chemotherapy that is likely to cause toxicity with little to no therapeutic effect. Pediatric hepatocellular carcinoma should not be evaluated and treated in the same manner

as adult hepatocellular carcinoma because these tumors arise in different settings. It is unknown if the biology of pediatric tumors are the same as or different from the lesions that occur in adults. Lesions from other malignancies that arise in both pediatric and adult populations suggest there is likely to be different biology requiring distinct therapeutic strategies for both groups. Therefore, in hepatocellular carcinoma it would seem that separate transplant criteria need to be established for pediatric patients to offer them the optimal chance at survival.

Chemoembolization, radiofrequency ablation, and cryosurgery are alternative methods that have been used in adult trials and have demonstrated the ability to cause decrease in liver tumor size. There are rare reports on the use of these techniques in pediatric patients (Malogolowkin et al. 2000). The identification of effective therapies against hepatocellular carcinoma is essential to improving the dismal outcomes for these patients.

Rhabdoid tumor of the liver has a poor prognosis even when resected. Different chemotherapy regimens have been used, and there has been evidence of chemosensitivity, with ifosfamide being potentially recognized as the most active agent (Katzenstein et al. 2003a). However, there is no established chemotherapeutic regimen that is effective in producing long-term survival for these patients. Undifferentiated sarcoma of the liver is usually treated with a sarcoma-based approach with surgery and chemotherapy (Baron et al. 2007).

Radiation therapy has no definitive role in the treatment of malignant liver tumors and has been mostly used in palliative care settings (Habrand et al. 1992).

36.7 Outcome

Surgical resection is critical to survival in patients with pediatric liver tumors. Patients with hepatoblastoma or hepatocellular carcinoma that are resected have excellent survival, while those that are unable to undergo surgical eradication of disease do poorly. Chemotherapy can result in tumor shrinkage that can often make resection feasible in children with hepatoblastoma, while this is rarely achievable in patients with hepatocellular carcinoma. Metastatic disease remains an adverse prognostic factor and predicts a poor outcome in all affected patients.

Table 36.2 Common liver tumors

Benign tumors	*Age at presentation*
Mesenchymal hamartoma	<5 years (usually infancy)
Teratoma	<5 years (usually infancy)
Hepatic adenoma	Older children and adolescents
Focal nodular hyperplasia	Older children and adolescents
Malignant tumors	
Hepatoblastoma	<5 years (usually infancy)
Hepatocellular carcinoma	Older children and adolescents
Sarcomas	Older children and adolescents
Metastatic disease	Any age

36.8 Practical Strategy for Liver Tumors

This discussion has centered on the diagnosis and treatment of malignant liver tumors. However, there are many benign tumors that present in childhood and adolescent. Many are only seen in infants and toddlers. Both malignant and benign liver tumors may be age specific (Table 36.2). A practical strategy for diagnosis of liver tumors is described. Many benign tumors have characteristic imaging findings. Biopsy is not always needed and may be detrimental, especially given a highly vascular lesion. Careful observation may be appropriate. A careful understanding of the natural history of the more common benign hepatic tumors of childhood is warranted (Table 36.3). A more complex issue is the treatment strategy for hepatoblastoma. In the US (COG), an attempt is made to perform initial resection at diagnosis for PRETEXT I and II tumors. Some patients will not need chemotherapy, for example stage I with pure fetal histology (Malogolowkin 2011). Others would need only two cycles. In the SIOPEL strategy, neoadjuvant chemotherapy is administered to the vast majority of patients (Perilongo et al. 2009). This may improve event-free survival, but all patients receive increased cisplatin and are at risk for late toxicity. Both COG and SIOPEL are working together for future strategies that may increase survival and lessen toxicity. Biological studies might greatly inform investigators on which patients need more or less therapy. The SIOPEL strategy, as a model of international collaboration, is described below.

Table 36.3 Management of benign liver tumors

Tumor	Diagnosis	Treatment
Infantile hepatic hemangioma	• Most common benign tumor in infancy • Contrast-enhanced CT findings – diagnostic • May be able to avoid biopsy	• Can have spontaneous remission • Steroids, IFN • Surgery should be reserved for life-threatening cases
Kaposiform hemangioendothelioma	• Rare, benign but behaves aggressively, may have true Kasabach-Merritt with platelet and factor consumption	• IFN • Multidrug regimens with vincristine, cyclophosphamide, actinomycin D, and methotrexate
Mesenchymal hamartoma	• Abdominal mass in healthy child • Right lobe most affected • CT shows multiple cysts, rare solid • AFP may be slightly elevated	• Surgery may be the only option • Medical treatment – debatable
Focal nodular hyperplasia	• Any age, but usually 2–5 years • Associated with syndromes such as Klinefelter's • Associated with past chemotherapy treatment • CT angiography/MRI – well demarcated, hyperachoic, homogenous	• Surgical treatment • Questionable role for arterial embolization

The SIOPEL Studies

(Michela Casanova)

If it is true that pediatric oncologists have been able to develop national multicenter and ultimately international cooperative protocols only for those tumors that could be considered more common in pediatric age, but not for very rare histotypes, that remains therefore "orphan diseases" with no standardized diagnostic and therapeutic guidelines, hepatoblastoma may be seen as the exception to the rule. The SIOPEL group, in fact, is a clear successful model of coordinated studies on very rare diseases. The SIOPEL 1 study was conducted between 1990 and 1994 and consisted of preoperative chemotherapy with a combination of cisplatin and doxorubicin (PLADO chemotherapy) followed by delayed surgery and further chemotherapy (Pritchard et al. 2000). Between 1994 and 1998, the SIOPEL 2 study tested chemotherapy with cisplatin alone in standard-risk hepatoblastoma, with encouraging results (90% response rate, 89% progression-free survival rate) (Perilongo et al. 2004). On the basis of this data, a prospective, randomized trial – the SIOPEL 3 (1998–2006) – compared the classic PLADO regimen (129 patients randomized) versus cisplatin alone (126 patients randomized) in patients with standard-risk hepatoblastoma. The final analysis showed that the cisplatin monotherapy achieved similar rates of complete resection and survival, thus suggesting that doxorubicin can be safely omitted from the treatment of standard-risk hepatoblastoma (Perilongo et al. 2009). Noteworthy, 92 institutions from 24 countries participated in the randomized study: These were countries from Western and Eastern Europe, from Middle East (i.e., Israel), from Central (i.e., Cuba) and South America (i.e., Argentina), and from Oceania (Australia and New Zealand). The SIOPEL history demonstrates how international cooperation can work – leading even to successful randomized trials in very rare tumors.

In patients with unfavorable prognosis (i.e., PRETEXT-IV, that means tumor involving all four hepatic sections, distant metastases, tumor extension into the vena cava or all three hepatic veins or tumor extension into the main and/or

both branches of the portal vein, or extrahepatic intra-abdominal disease, and also initial low serum AFP or tumor rupture at presentation), the SIOPEL explored the role of chemotherapy intensification, with the addition to carboplatin to the PLADO backbone (with chemotherapy cycles given every 14 days and not every 21 days as for classic PLADO). The SIOPEL-3HR study was conducted between 1998 and 2004, involving 22 different countries and a total of 151 patients. As main results, the intensified treatment was able to achieve a partial response in around 80% of cases (and complete remission of the lung metastases with chemotherapy alone in half of the cases), to render a great proportion of tumors resectable (76% of cases), and – in comparison to previous results – led to an improved survival in patients with high-risk hepatoblastoma, with a 3-year overall survival of 69% and 62% on patients with PRETEXT-IV tumor and with initial metastases, respectively (Zsíros et al. 2010). A further intensification, with a preoperative chemotherapy with weekly cisplatin associated to doxorubicin, has been evaluated in the SIOPEL 4 study, recently closed (the results are not yet available), while a study evaluating the role of sodium thiosulphate in reducing hearing loss associated to cisplatin chemotherapy (SIOPEL 6 study) is ongoing.

Concerning hepatocellular carcinoma, SIOPEL results were less satisfactory: In particular, the carboplatin intensification, with dose-density chemotherapy, did not improve survival rates (3-year overall survival of 22%). The SIOPEL 5 study was the first international study designed for children, adolescents, and young adults with non-cirrhotic hepatocellular carcinoma: The main strategy was the use of standard neoadjuvant PLADO chemotherapy in combination with thalidomide (an antiangiogenic agent) for unresectable cases and the use of low-dose metronomic chemotherapy as adjuvant treatment to investigate whether this might reduce the risk of recurrence following resection. Unfortunately, this study failed for inadequate accrual. A similar study based on the use of sorafenib is under preparation (Llovet et al. 2008).

References

Abou-Alfa GK, Johnson P et al (2010) Doxorubicin plus sorafenib vs. doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. JAMA 304(19):2154–2160

Aronson DC, Schnater JM et al (2005) Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. J Clin Oncol 23(6):1245–1252

Baron PW, Majlessipour F et al (2007) Undifferentiated embryonal sarcoma of the liver successfully treated with chemotherapy and liver resection. J Gastrointest Surg 11(1): 73–75

Beaty O 3rd, Berg S et al (2010) A phase II trial and pharmacokinetic study of oxaliplatin in children with refractory solid tumors: a Children's Oncology Group study. Pediatr Blood Cancer 55(3):440–445

Blohm ME, Vesterling-Horner D et al (1998) Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol 15(2):135–142

Buckley JD, Sather H et al (1989) A case-control study of risk factors for hepatoblastoma. A report from the Childrens Cancer Study Group. Cancer 64(5):1169–1176

Chang MH, Chen CJ et al (1997) Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 336(26):1855–1859

Clericuzio CL, Chen E et al (2003) Serum alpha-fetoprotein screening for hepatoblastoma in children with Beckwith-Wiedemann syndrome or isolated hemihyperplasia. J Pediatr 143(2):270–272

Czauderna P (2002) Adult type vs. Childhood hepatocellular carcinoma – are they the same or different lesions? Biology, natural history, prognosis, and treatment. Med Pediatr Oncol 39(5):519–523

Czauderna P, Mackinlay G et al (2002) Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology group. J Clin Oncol 20(12):2798–2804

Darbari A, Sabin KM et al (2003) Epidemiology of primary hepatic malignancies in U.S. children. Hepatology 38(3):560–566

DeBaun MR, Tucker MA (1998) Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. J Pediatr 132(3 Pt 1):398–400

Exelby PR, Filler RM et al (1975) Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey – 1974. J Pediatr Surg 10(3):329–337

Haas JE, Feusner JH et al (2001) Small cell undifferentiated histology in hepatoblastoma may be unfavorable. Cancer 92(12):3130–3134

Habrand JL, Nehme D et al (1992) Is there a place for radiation therapy in the management of hepatoblastomas and hepatocellular carcinomas in children? Int J Radiat Oncol Biol Phys 23(3):525–531

Hirschman BA, Pollock BH et al (2005) The spectrum of APC mutations in children with hepatoblastoma from familial adenomatous polyposis kindreds. J Pediatr 147(2):263–266

Jassam N, Jones CM et al (2006) The hook effect: a need for constant vigilance. Ann Clin Biochem 43(Pt 4):314–317

Katzenstein HM, Krailo MD et al (2002) Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. J Clin Oncol 20(12):2789–2797

Katzenstein HM, Kletzel M et al (2003a) Metastatic malignant rhabdoid tumor of the liver treated with tandem high-dose therapy and autologous peripheral blood stem cell rescue. Med Pediatr Oncol 40(3):199–201

Katzenstein HM, Krailo MD et al (2003b) Fibrolamellar hepatocellular carcinoma in children and adolescents. Cancer 97(8):2006–2012

Lin CY, Kuo CS et al (2010) Elevated serum vitamin B(12) levels in association with tumor markers as the prognostic factors predictive for poor survival in patients with hepatocellular carcinoma. Nutr Cancer 62(2):190–197

Llovet JM, Ricci S, et al (2008) SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. Jul 24;359(4):378–90

Malogolowkin MH, Stanley P et al (2000) Feasibility and toxicity of chemoembolization for children with liver tumors. J Clin Oncol 18(6):1279–1284

Malogolowkin MH, Katzenstein HM et al (2008) Redefining the role of doxorubicin for the treatment of children with hepatoblastoma. J Clin Oncol 26(14):2379–2383

Malogolowkin MH, Katzenstein HM, Krailo M, Rowland J, Haas J, Meyers RL, Finegold M (2011) Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology. J Clin Oncol 29(24): 3301–3306

Meyers RL, Katzenstein HM et al (2007) Surgical resection of pulmonary metastatic lesions in children with hepatoblastoma. J Pediatr Surg 42(12):2050–2056

Ortega JA, Douglass EC et al (2000) Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. J Clin Oncol 18(14): 2665–2675

Otte JB, Pritchard J et al (2004) Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. Pediatr Blood Cancer 42(1):74–83

Perilongo G, Shafford E et al (2004) Risk-adapted treatment for childhood hepatoblastoma. Final report of the second study of the International Society of Paediatric Oncology–SIOPEL 2. International Society of Paediatric Oncology-SIOPEL 2. Eur J Cancer. Feb;40(3):411–21

Perilongo G, Maibach R et al (2009) Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 361(17):1662–1670

Pritchard J, Brown J et al (2000) Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach – results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 18(22):3819–3828

Prokurat A, Kluge P et al (2002) Transitional liver cell tumors (TLCT) in older children and adolescents: a novel group of aggressive hepatic tumors expressing beta-catenin. Med Pediatr Oncol 39(5):510–518

Qayed M, Powell C et al (2010) Irinotecan as maintenance therapy in high-risk hepatoblastoma. Pediatr Blood Cancer 54(5):761–763

Ries LAG SM, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) (1999) Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. National Cancer Institute, Bethesda, SEER Program NIH Publication No. 99–4649

Ross JA, Gurney JG (1998) Hepatoblastoma incidence in the United States from 1973 to 1992. Med Pediatr Oncol 30(3):141–142

Rowland JM (2002) Hepatoblastoma: assessment of criteria for histologic classification. Med Pediatr Oncol 39(5):478–483

Spector LG, Feusner JH et al (2004) Hepatoblastoma and low birth weight. Pediatr Blood Cancer 43(6):706

Trobaugh-Lotrario AD, Tomlinson GE et al (2009) Small cell undifferentiated variant of hepatoblastoma: adverse clinical and molecular features similar to rhabdoid tumors. Pediatr Blood Cancer 52(3):328–334

Van Tornout JM, Buckley JD et al (1997) Timing and magnitude of decline in alpha-fetoprotein levels in treated children with unresectable or metastatic hepatoblastoma are predictors of outcome: a report from the Children's Cancer Group. J Clin Oncol 15(3):1190–1197

von Schweinitz D, Byrd DJ et al (1997) Efficiency and toxicity of ifosfamide, cisplatin and doxorubicin in the treatment of childhood hepatoblastoma. Study Committee of the Cooperative Paediatric Liver Tumour Study HB89 of the German Society for Paediatric Oncology and Haematology. Eur J Cancer 33(8):1243–1249

Wu JT, Book L et al (1981) Serum alpha fetoprotein (AFP) levels in normal infants. Pediatr Res 15(1):50–52

Zsíros J, Maibach R et al (2010) Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study J Clin Oncol. 2010 May 20;28(15):2584–90. Epub Apr 20

Paediatric Peritoneal Mesothelioma

37

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37.1 Introduction

Malignant mesothelioma is an aggressive tumour that originates from the surface mesothelial layer covers the serosal surfaces, such as the pleura, the peritoneum or more rarely the tunica vaginalis testis and the pericardium (Moore et al. 2008). Before the 1950s, the existence of adults' mesothelioma was questioned by many pathologists (Moore et al. 2008). Nevertheless, the increase in the incidence of mesothelioma, following the growing use of asbestos, definitely established mesothelioma as a real disease (Margery and Ruffié 2008). In children, because this is an extremely rare tumour, some paediatric oncologists still doubt of its existence. Moreover, the diagnosis is appreciated as being difficult, and many cases that were reported as paediatric mesothelioma were not confirmed by recent second pathological analysis (Antman et al. 1984). Nevertheless, recently, small series have been published with the use of state of the art adults' diagnosis criteria (Moran et al. 2008).

We will focus here on peritoneal mesothelioma and exclude pleural mesothelioma (which is presented in a separate chapter 27, we also exclude mesothelioma of the tunica vaginalis testis and pericardial mesothelioma).

To decide on the optimal treatment for individual patients and to try to increase our knowledge on this disease to understand its biological basis still represent great challenges for those involved with patient care, particularly paediatric oncologists.

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37.2 Epidemiology

Peritoneal mesothelioma is an extremely rare disease in children, and no precise epidemiological data on the incidence of this disease are available. Our knowledge is mainly based on case reports, and the first paediatric series was published in 1964 (Kauffman and Stout 1964). According to autopsies' results, paediatric mesothelioma should represent 2–5% of all mesothelioma cases, and according to epidemiologic studies would represent 0.5–1.0 case/10 millions/year (Kashanskiy and André 2010). We previously reviewed and reported epidemiologic data of 489 cases of paediatric mesothelioma and peritoneal mesothelioma accounted for one-fourth among these cases, in line with another less extensive previous review of the literature (Kauffman and Stout 1964). As in adults, there is a higher frequency of peritoneal mesothelioma in girls (Kauffman and Stout 1964) with a female/male ratio of 2:1 (Kashanskiy and André 2010). The mean age at presentation was 11.9 ± 0.6 years with no difference between sexes (Kashanskiy and André 2010). An unusual case of peritoneal mesothelioma occurred in a 6-week-old girl (Silberstein et al. 1983).

Although a strong link with prior exposure to asbestosis and mesothelioma is well known and generally accepted (Moore et al. 2008), in our experience, there was no association with asbestos exposure in children. Only four children had a confirmed previous exposure to asbestos among the 50 cases for which the exposure to asbestos was documented (Kashanskiy and André 2010). Similarly, the reported paediatric cases with a prior exposure to asbestos are anecdotal, and in many countries in which the exposure to asbestos is high because of the presence of mines like in Australia, no cases have been reported. Moreover, as it usually takes 20 years or longer after asbestos exposure to develop mesothelioma, it seems very unlikely that asbestosis is implicated in the pathogenesis of mesothelioma in children and more specifically for peritoneal mesothelioma. Thus, most paediatric mesothelioma cases might be idiopathic forms of mesothelioma, which can also occur in adults with an incidence of one per million (Moore et al. 2008).

Furthermore, other predisposing factors have been proposed for childhood mesothelioma such as irradiation and genetic syndromes. These hypotheses are based on reported cases of paediatric mesothelioma developing after irradiation (Stock et al. 1979; Anderson et al. 1985; André et al. 2009), as secondary malignancies especially after Wilms' tumour and Hodgkin disease (Anderson et al. 1985; André et al. 2009; Falchero et al. 1996; Antman et al. 1984) or in children with Proteus syndrome (Gordon et al. 1995; Malamitsi-Puchner et al. 1990). Indeed, these cases suggest that an underlying genetic background may contribute to the occurrence of a mesothelioma in these affected patients. Mutation of WT1 has been reported in sporadic cases of mesothelioma, but the role of this gene in the genesis and progression of the tumour is not clear yet (Park et al. 1993). Some familial cases of mesothelioma have been reported with a deletion of the short arm of chromosome 9 that carry the CDKN2A gene. This gene encodes for $p16^{INK4a}$ and $p14^{ARF}$, and inactivation of these oncoproteins has been frequently reported in mesothelioma (You et al. 2007; Ugolini et al. 2008). Nevertheless, no children have been reported to be affected in these familial series. More recently, functional mutations were detected in EGFR in 31% of peritoneal mesothelioma. All mutations are clustered near the ATP-binding cleft of the tyrosine kinase domain. However, it still remains to be further studied, whether these mutations represent gatekeeper events in the development of peritoneal mesothelioma or be a mere secondary event occurring during later progression of the disease (Foster et al. 2010). Similarly, the therapeutic impact of these findings remains an issue for future clinical studies.

37.3 Clinical Presentation

A long delay is usually observed between the appearance of the first clinical signs and diagnosis. Peritoneal mesothelioma typically presents with unspecific symptoms such as weight loss, abdominal distension and ascites in which ascites represented the most common initial clinical finding (Antman et al. 1984; Moran et al. 2008; Kauffman and Stout 1964; André et al. 2009; Fraire et al. 1988). As tumours grow, pain and extension to other serosal surfaces may be seen. In a paediatric series, 3 out of 12 patients displayed involvement of more than one serosal surface (André et al. 2009).

37.4 Radiological Presentation

Malignant peritoneal mesothelioma tends to spread in sheets of tissue over the parietal and visceral peritoneal surfaces and to become confluent, thereby encasing the abdominal organs. In such cases, extensive lesions may be accompanied by ascites. The CT features of malignant peritoneal mesotheliomas range from a "dry"

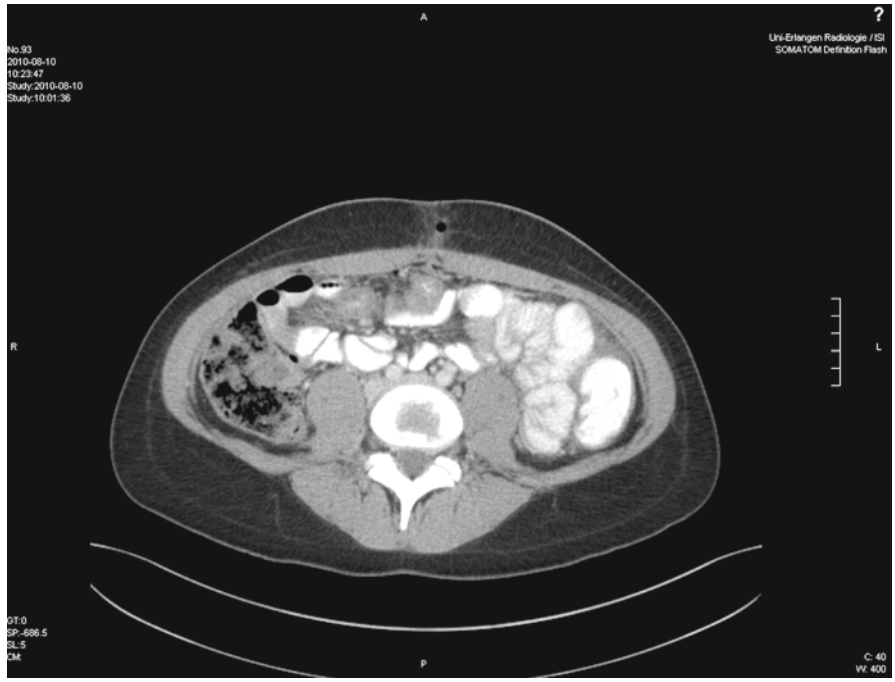

Fig. 37.1 CT-scan of a 16-year-old girl with peritoenal mesothelioma Solid and cystic tumourous masses occupying the pelvic cavity seem to involve the ovaries. There is accumulation of ascitic fluid between the liver and the diaphragm and in the precardial and the ileocecal region. Note also some prominent mesenteric lymph nodes

appearance, consisting of peritoneum-based masses, to a "wet" appearance, consisting of ascites, irregular or nodular peritoneal thickening, and one or several omental masses. The latter is the most frequent presentation in children (Silberstein et al. 1983; Terry and Fowler 2009; Milano et al. 2006). Scalloping or direct invasion of adjacent abdominal organs can also be seen (Milano et al. 2006). Frequently, CT appears as a multilocular cystic mass. Cystic mesothelioma typically consists of multiple grape-like clusters of mesothelium-lined cysts. In our experience, the bulky tumour may be more extensive in the pelvic peritoneum, thereby extending into the ovaries. This may, in part, result in the under-recognition of peritoneal mesothelioma in females and its misinterpretation as advanced ovarian cancer.

Although FDG-PET is not reliable in detecting non-bulky tumour growth in the peritoneum, it is a useful modality to explore a peritoneal mesothelioma in children. It can also show metabolic active components within cystic lesions (Milano et al. 2006).

37.5 Pathology

The pathological diagnosis of mesothelioma is recognised as difficult. As for adults, pathologic analysis should be performed on specimen obtained by surgery and not on limited needle biopsies. All cases should also be confirmed by a panel of pathologists including one with experience in adult mesothelioma and the application of an appropriate panel of immunohistochemical stains. Grossly, the tumours showed multiple, diffuse or confluent peritoneal nodules or larger masses. Histologically, in a series of eight cases (Moran et al. 2008), most cases corresponded to epithelioid mesotheliomas, and one case displayed biphasic (epithelioid and spindle) cellular pattern. In our review, we also found that a majority of peritoneal mesotheliomas were of the epithelioid type regardless of age and sex (Kashanskiy and André 2010) (Figs. 37.1–37.4 Table 37.1).

On scanning magnification, the tumour classically displays sheets of medium-sized or large epithelioid cells with well-developed tubulo-papillary structures. At higher magnification, the tumour cells display bland cytological appearance composed of polygonal cells with moderate amount of pale eosinophilic frequently vacuolated cytoplasm, round nuclei and inconspicuous nucleoli. Usually, only rare mitotic figures can be identified ($<1/mm^2$). In some areas, the epithelioid cells could be seen within an abundant mucinous or myxoid stroma (Moran et al. 2008; Silberstein et al. 1983). A few scattered psammoma bodies are frequently seen, particularly in tumours with prominent papillary pattern. This feature together with others represents a pitfall in the diagnosis of peritoneal mesothelioma in women and girls and probably suggests misinterpretation of some cases as serous carcinomas of the ovaries

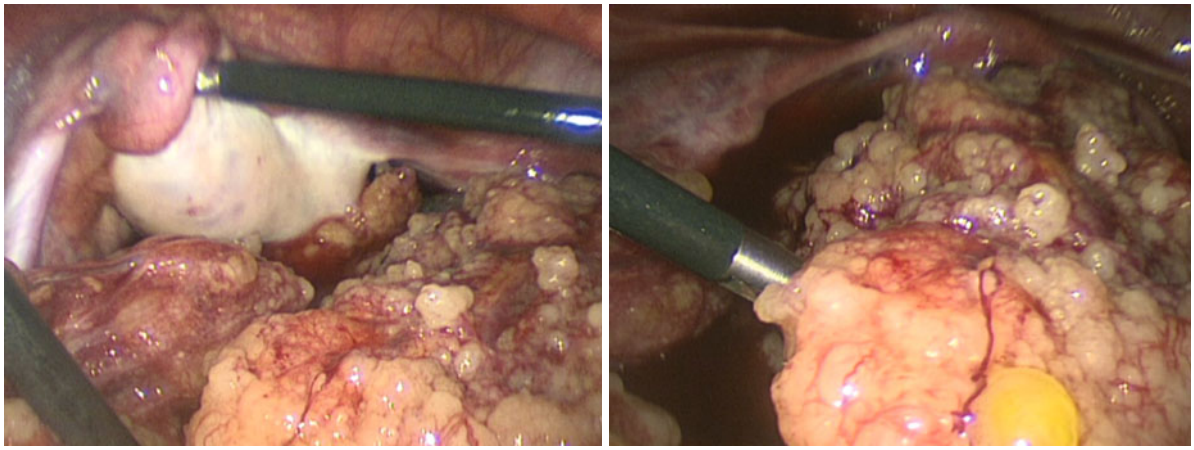

Fig. 37.2 Intra-operative laparoscopic view: confluent nodular masses involve the whole greater omentum and both ovaries. In the right lower abdomen thickened cysts with evidence of torsion, bleeding and partial rupture are seen

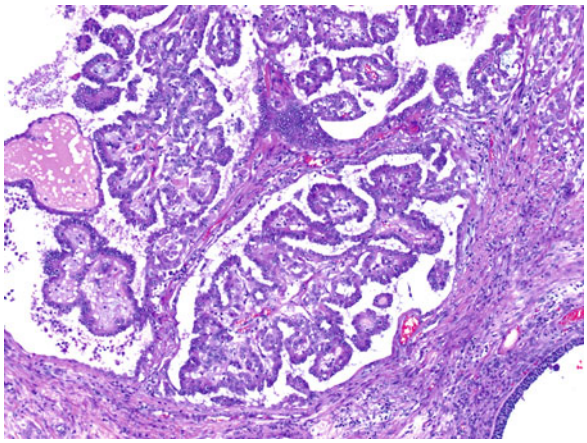

Fig. 37.3 Histological features: mesothelioma tissue composed of characteristic tubulopapillary structures is seen within the ovary adjacent to a follicle cyst (*lower right*). This finding closely mimics serous ovarian cancer and may be misdiagnosed if mesothelioma is not thought of

(Figs. 37.3). Accordingly, we suspect that peritoneal mesotheliomas in children and young women might be under-diagnosed by general pathologist who is unfamiliar with the histology of adult mesothelioma.

Classical immunohistochemical studies for cytokeratin (CK) 5/6 and low molecular weight CK (CAM5.2) show strong cytoplasmic positivity in the neoplastic cells. In addition, peritoneal mesothelioma expresses vimentin, calretinin, podoplanin (D2-40), mesothelin, HMBE-1 and WT1 (Figs. 37.4). It is noteworthy that WT1, CK7 and CA12.5 are regularly expressed both in mesothelioma and serous carcinoma and are thus of no value in their distinction. PAX8 is a recent marker that is expressed in the nuclei of serous carcinomas but not in mesothelioma. Similarly, some keratin markers, Ber-EP4 and carcinoembyronic antigen (CEA), are regularly negative in mesothelioma.

Besides, one should be aware of an even rarer entity called multicystic mesothelioma of the peritoneum. This rare benign or indolent tumour commonly occurs in young to middle aged women and also may affect children. The classic signs and symptoms are abdominal pain, tenderness or distension with an abdominal or pelvic mass. The lesion is composed of fluid-filled thin-walled cystic spaces lined by flat cuboidal mesothelial cells that may confluent to a large multicystic mass or even spread along the peritoneal surface. Multiple recurrences can occur (Terry and Fowler 2009) as well as malignant degeneration (Milano et al. 2006). Accordingly, surgical removal of this rare tumour should be attempted and the patient carefully monitored. Multicystic mesothelioma should therefore be distinguished from focal cystic areas within malignant peritoneal mesothelioma.

37.6 Treatment and Outcome

In adults, no standard treatment strategy is currently available owing to the rarity of this tumour, which is even rarer in young children. Recent data (Moran et al. 2008; André et al. 2009; Milano et al. 2006; Cioffredi et al. 2009) suggest that the prognosis of these patients is far better than what was generally believed with

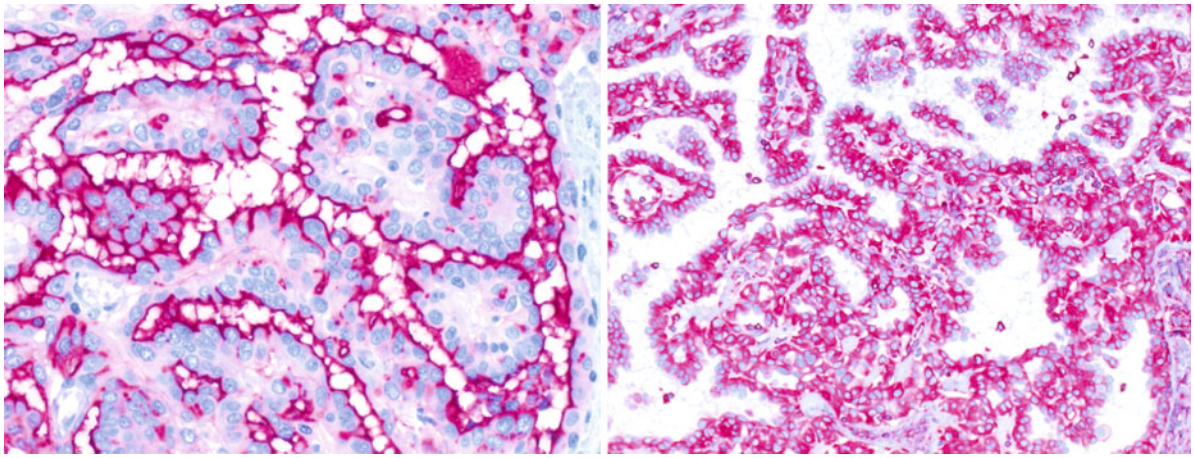

Fig. 37.4 In addition to expression of typical immunohistochemical mesothelioma markers (D2-40, *left* image), detection of the mesenchymal marker vimentin (*right* image) in a papillary ovarian neoplasm strongly suggests mesothelioma

Table 37.1 Key points to manage a child with perintoneal mesothelioma

Physical examination	Signs and symptoms (constipation/diarrhoea, tenesmus, bowel obstruction, fatigue, weight loss) Clinical history: asbestosis exposure
Laboratory assessment	Non-specific
Radiological assessment	
– First assessment	Abdominal ultrasound
– Local staging	Abdominal computed tomography (CT) scan Surgical staging
Diagnostic work	Chest and abdominal CT scan, positron emission tomography (PET)
Pathological assessment	– Surgical biopsy required – Confirmation of diagnosis by pathologist/s with experience in adult´s mesothelioma always necessary – Confirm the diagnosis of malignant mesothelioma and subtype – Application of an appropriate panel of immunohistochemical stains
Staging systems for risk-adapted treatment strategy	None validated
General treatment guidelines	– Need for multidisciplinary approach – Seek for national and/or European group for rare tumours advice – Seek advice from centre with expert physicians professionally dedicated to the management of this cancer in adults
– Surgery	– Keystone of treatment – Consider multivisceral resections, peritonectomy or procedures as hyperthermic intraperitoneal chemoperfusion (HIPEC)
– Radiotherapy	None
– Chemotherapy	– First line : pemetrexed–cisplatinum – Second line or alternative : gemcitabine–pemetrexed – Consider chemotherapy with novel agents for advanced disease validated in adults

mesothelioma. Using multimodal approach, in the SFCE series of paediatric mesothelioma, all eight patients with peritoneal mesothelioma were alive with a mean follow up of 61 months, following multimodal therapy and often several lines of chemotherapy (André et al. 2009).

Similar findings have been reported elsewhere (Cioffredi et al. 2009). Nevertheless, paediatric peritoneal mesotheliomas have an unpredictable biologic behaviour, requiring individual treatment strategies.

37.6.1 Surgery

Surgery aiming at removal of all malignant tissue is only very rarely associated with persistent durable complete remission as the disease is usually, at least microscopically, spread within the peritoneal cavity. Therefore, we advocate for complete surgery only in cases of easily removable tumour. If complete remission cannot be achieved without sequelae, debulking surgery is another option and should be then followed by chemotherapy. An interesting alternative is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy which is gaining interest in adults (Yan et al. 2009) and can yield sustained remissions in children (André et al. 2009).

37.6.2 Chemotherapy

While the combination of pemetrexed–cisplatinum is a standard in adults with pleural mesothelioma (Vogelzang et al. 2003), there is currently no standard chemotherapy regimen for peritoneal mesothelioma. Nevertheless, a combination of gemcitabine and pew metrexed has recently been reported to have an interesting efficacy in adults with peritoneal mesotheliomas (Simon et al. 2008) and could be used for children, too. Moreover, these new molecules (pemetrexed, gemcitabine) indeed seem to bring clinical benefit to children with mesothelioma (André et al. 2009; Milano et al. 2006; Cioffredi et al. 2009).

37.6.3 Radiotherapy

Radiotherapy has not been demonstrated to be an effective treatment in mesothelioma, and its use is limited to control disease in palliative setting.

37.6.4 Targeted Therapy

As to date, there is no specific therapy that targets molecular pathways in malignant mesothelioma. This is because the major molecular mechanisms involved in the initiation, development and progression of mesothelioma are still largely unknown. A recent study has demonstrated the occurrence of novel oncogenic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) in 31% of cases of peritoneal mesothelioma investigated (Foster et al. 2010). In that study, the presence of EGFR mutation appeared to predict response to therapy with erlotinib in cell line experiments. Despite the disappointing initial results in adults, this new observation might open a new hope and option as part of multi-agent therapy for affected patients including children, but this remains to be confirmed in larger controlled clinical studies.

37.7 Conclusion

Mesothelioma is a very rare tumour in paediatric oncology. Paediatric mesothelioma seems to be different from its adult counterpart with less frequent primary pleural localization. The outcome of children with peritoneal mesothelioma is good despite frequent relapses by using effective treatment (multimodal therapy, the use of recent cytotoxic agents, hyperthermic intraperitoneal chemotherapy). These strategies need to be properly evaluated in children, and an international registry is mandatory to increase our knowledge of this disease. Thus, we encourage reporting cases of mesothelioma in children to national registries for rare paediatric tumours and choosing an interdisciplinary and international approach in the management of these extremely rare entities.

References

Anderson KA, Hurley WC, Hurley BT et al (1985) Malignant pleural mesothelioma following radiotherapy in a 16-year-old boy. Cancer 56:273–276

André N, Ratsimandresey R, Réguerre Y et al (2009) Paediatric malignant mesothelioma: the SFCE experience. Pediatr Blood Cancer 53:823

Antman KH, Ruxer RL Jr, Aisner J et al (1984) Mesothelioma following Wilms' tumor in childhood. Cancer 54:367–369

Cioffredi LA, Jänne P, Jackman D (2009) Treatment of peritoneal mesothelioma in pediatric patients. Pediatr Blood Cancer 1:127–129

Falchero L, Coiffier B, Guibert B et al (1996) Malignant mesothelioma of the pleura following radiotherapy for Hodgkin disease. Bull Cancer 83:964–968

Foster JM, Radhakrishna U, Govindarajan V et al (2010) Clinical implications of novel activating EGFR mutations in malignant peritoneal mesothelioma. World J Surg Oncol 8:88

Fraire AE, Cooper S, Greenberg SD et al (1988) Mesothelioma of childhood. Cancer 62:838–847

Gordon PL, Wilroy RS, Lasater OE et al (1995) Neoplasms in Proteus syndrome. Am J Med Genet 57:74–78

Kashanskiy SV, André N (2010) Paediatric mésothelioma: is there such a disease? Bull Cancer 97:571–576

Kauffman SL, Stout AP (1964) Mesothelioma in children. Cancer 17:539–544

Malamitsi-Puchner A, Dimitriadis D, Bartsocas C et al (1990) Proteus syndrome: course of a severe case. Am J Med Genet 35:283–285

Margery J, Ruffié P (2008) Environmental cancer: malignant pleural mesothelioma. Bull Cancer 95:77–86

Milano E, Pourroy B, Rome A, Delarue A, Coze C, Gorincour G, Bouvier C, Braguer D, André N (2006) Efficacy of a combination of pemetrexed and multiple redo-surgery in an 11-year-old girl with a recurrent multifocal abdominal mesothelioma. Anticancer Drugs 17:1231–1234

Moore AJ, Parker RJ, Wiggins J (2008) Malignant mesothelioma. Orphanet J Rare Dis 3:34

Moran CA, Albores-Saavedra J I, Suster S (2008) Primary peritoneal mesotheliomas in children: a clinicopathological and immunohistochemical study of eight cases. Histopathology 52:824–830

Park S, Schalling M, Bernard A, Maheswaran S, Shipley GC, Roberts D, Fletcher J, Shipman R, Rheinwald J, Demetri G et al (1993) The Wilms tumour gene WT1 is expressed in murine mesoderm-derived tissues and mutated in a human mesothelioma. Nat Genet 4:415–420

Silberstein MJ, Lewis JE, Blair JD, Graviss ER, Brodeur AE (1983) Congenital peritoneal mesothelioma. J Pediatr Surg 18:243–245

Simon GR, Verschraegen CF, Jänne PA et al (2008) Pemetrexed plus gemcitabine as first-linechemotherapy for patients with peritoneal mesothelioma: final report of a phase II trial. J Clin Oncol 26:3567–3572

Stock RJ, Fu YS, Carter JR (1979) Malignant peritoneal mesothelioma following radiotherapy for seminoma of the testis. Cancer 44:914–919

Terry NE, Fowler CL (2009) Benign cystic mesothelioma in a child. J Pediatr Surg 44:e9–e11

Ugolini D, Neri M, Ceppi M et al (2008) Genetic susceptibility to malignant mesothelioma and exposure to asbestos: the influence of the familial factor. Mutat Res 658:162–167

Vogelzang NJ, Rusthoven JJ, Symanowski J et al (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636–2644

Yan TD, Deraco M, Baratti D et al (2009) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol 27:6237–6242

You B, Blandin S, Gérinière L et al (2007) Mésothéliomes familiaux: une composante génétique associée aux risques environnementaux ? Bull Cancer 7:705–710

Retroperitoneal Tumors

38

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38.1 Introduction

There are several rare retroperitoneal tumors that do not involve usual retroperitoneal organs, such as pancreas, kidneys, and adrenal glands, but derive from adipose, muscular, vessel, and nerve tissue in the retroperitoneal space. Though these tumors are not gastrointestinal tumors, we have included them in this section. They show different embryological origins and biology according to histotype. The majority of retroperitoneal tumors occur in the first 5 years of life (Young et al. 1986). The most common malignant retroperitoneal tumor is the neuroblastoma, which is not considered a rare pediatric tumor, they account for approx. 75% of cases of retroperitoneal tumors in children under the age of 15 years. A heterogeneous group of soft tissue sarcomas and germ cell tumors constitute the next common in incidence, though also "very rare" (see Figs. 38.1 and 38.2). The management of these entities are discussed in Chapters 44 and 39. Rare cases of retroperitoneal carcinosarcoma (Xu et al. 2010), malignant paraganglioma (Buonuomo et al. 2004), and extrarenal Wilms' tumor (Deshpande et al. 2002) have been described. Also, it is important to differentiate malignant tumors from benign cystic lesions and inflammatory and hemorrhagic conditions. We will present brief general remarks on differential diagnosis and management, specific for this area.

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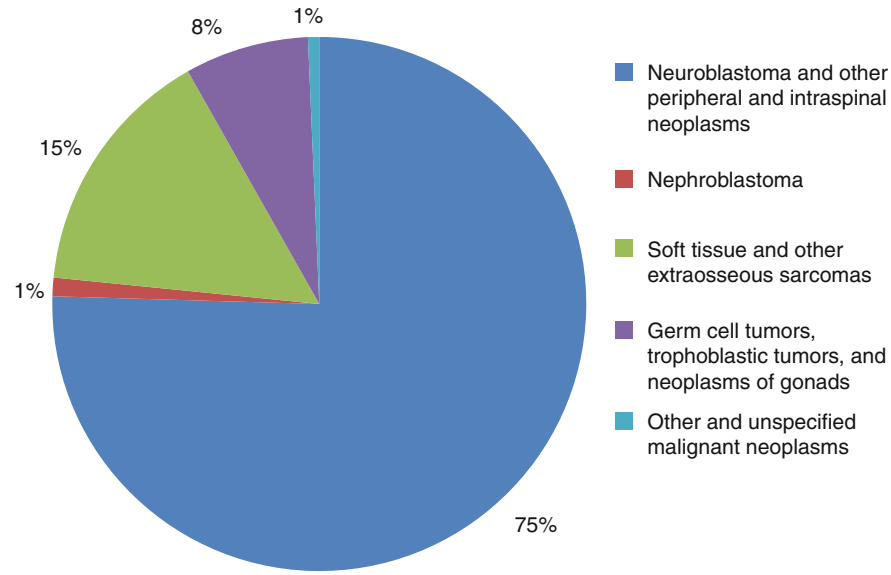

Fig. 38.1 Distribution of retroperitoneal tumors by ICCC-3 category in children under the age of 15 years (Data from the United States Surveillance and End Results Registry (SEER), 1973–2004)

38.2 Diagnosis

Signs and symptoms of retroperitoneal tumors are often subtle and nonspecific: abdominal and/or back pain, abdominal swelling, paresthesia of the lower extremities, venous swelling of the legs, weight loss, weakness, and anemia. It is crucial to differentiate whether the tumor arises from a retroperitoneal organ or not. Specific radiological findings have been described to assist in making a differential diagnosis. For example, calcifications would be suggestive for ganglioneuroma or malignant fibrohistocytoma, adipose tissue points to lipoma (homogenous) or liposarcoma (herterogeneous).

Hypervascularization is in hemangiomas and hemangioperizytoma, and areas of low homogeneous density in neurofibroma (Carbognin et al. 2005). Ultrasound can help ascertain the dimension of the tumor and determine the relationship to the vasculature. Additionally, MRI or CT-angiography, rather than CT alone, are recommended. Tumor markers can be very helpful for diagnosis, e.g., alpha-fetoprotein for teratoma. A biopsy must be performed if the tumor seems irresectable or resectable only by extended surgery.

38.3 Therapy

Retroperitoneal tumors are usually recognized late. The retroperitoneal anatomy is complex, and these tumors are often large at presentation. Therefore, these tumors pose a challenge for local and systemic control. Complete surgical resection is the mainstay of treatment in most cases. However, tumor-free margins are difficult to obtain and the local failure rate is high (Windham and Pisters 2005). It is crucial to determine resectability preoperatively, but involvement of adjacent vascular structures or organs is often difficult to ascertain with preoperative imaging. When planning surgery, the possible need for extensive en bloc resections and multivisceral resections should be taken into account. Depending on the histological entity, neoadjuvant chemo- and/or radiotherapy can be important to reach resectability.

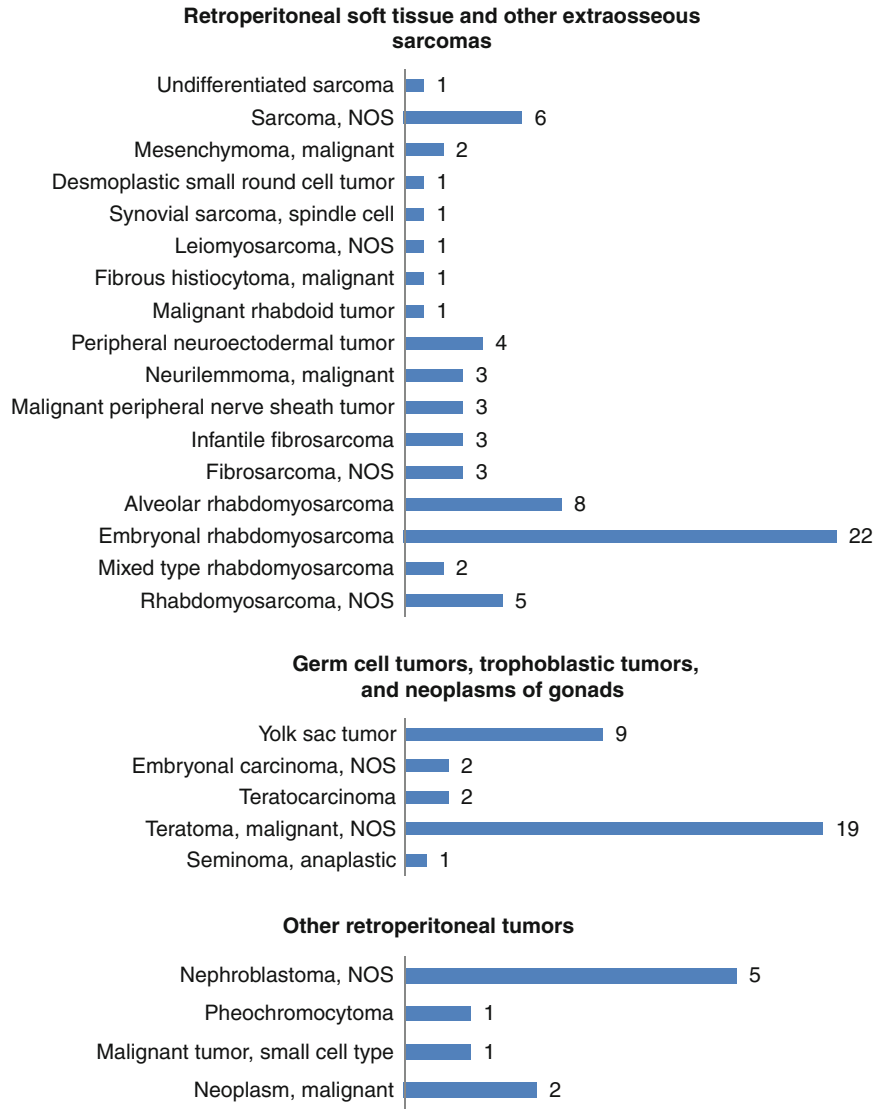

Fig. 38.2 Total number of retroperitoneal tumors in children under the age of 15 years registered with the United States Surveillance and End Results Registry (SEER), 1973–2004, by ICCC-3 category and histology (ICD-3) NOS = not other specified

For further information on treatment, please refer to the chapters "Rare Sarcomas" and "Germ Cell Tumors" within this book.

References

Buonuomo V, Ruggiero A et al (2004) Malignant retroperitoneal paraganglioma: case report and review of the literature. Pediatr Hematol Oncol 21(8):731–738

Carbognin G, Pinali L et al (2005) Retroperitoneal tumors. In: Gourtsoyiannis N, Ros P (eds) Radiologic-pathologic correlations from head to toe. Springer, Berlin/Heidelberg, pp 619–643

Deshpande AV, Gawali JS et al (2002) Extrarenal Wilm's tumour – a rare entity. Pediatr Surg Int 18(5-6):543–544

Windham TC, Pisters PW (2005) Retroperitoneal sarcomas. Cancer Control 12(1):36–43

Xu F, Huang Y et al (2010) Primary retroperitoneal carcinosarcoma in a child: a case report. World J Surg Oncol 8:99

Young JL Jr, Ries LG et al (1986) Cancer incidence, survival, and mortality for children younger than age 15 years. Cancer 58(2 Suppl):598–602

Part VIII

Germ Cell Tumors and Genitourinary Tumors

Gonadal and Extragonadal Germ Cell Tumors, Sex Cord Stromal and Rare Gonadal Tumors

39

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39.1 Overview on Epidemiology, Biology, Histology, and Clinic

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Germ cell tumors include a group of tumors that are highly heterogeneous regarding their clinical and histologic appearance. Altogether they comprise approximately 2–3% of cancers diagnosed in children and adolescents younger than 15 years (Ries LAG et al. 1999a; Kaatsch 2004a). During childhood and adolescence, approximately half of all germ cell tumors develop at extragonadal midline sites. Sacrococcygeal germ cell tumors constitute the most frequent tumor in neonates, and extracranial germ cell tumors account for 14% of all cancers in adolescents of the 15–19 age group. An epidemiological analysis of patients reported to the German GCT trials from 1981 to 2000 showed a bimodal age distribution with a small peak during infancy and a larger peak after puberty, to be continued among adults, among which germ cell tumors constitute the most common cancer in young men (Schneider et al. 2004a). During the first year of life, teratomas predominate, with a slight female preponderance (Fig. 39.1.1a, b). After the first 6 months of life, yolk sac tumors are the most frequent histologic subtype. This histology is slightly more often seen in boys than in girls. Tumors with germinoma histology (syn. seminoma or dysgerminoma) are first observed in girls at 5 years of age and show a gradually increasing incidence during adolescence. Seminomas are not seen in boys, until they reach puberty. The same accounts for other nongerminomatous histologies such as embryonal carcinoma and choriocarcinoma, which are mainly seen during and after puberty, in most cases as components of mixed malignant germ cell tumors (Fig. 39.1.1c) (Schneider et al. 2004a).

This bimodal age distribution is also demonstrated by the Surveillance Epidemiology and End Results Registry (SEER). Of note, there appears to be a significant increase of the incidence in specific subgroups such as adolescent boys and prepubertal girls (Poynter et al. 2010). This study suggests that the biology of germ cell tumors may differ between different populations and clinical subgroups.

Separate groups are marked by distinct clinical and molecular features. The distribution of gonadal and extragonadal tumor sites by age is shown in

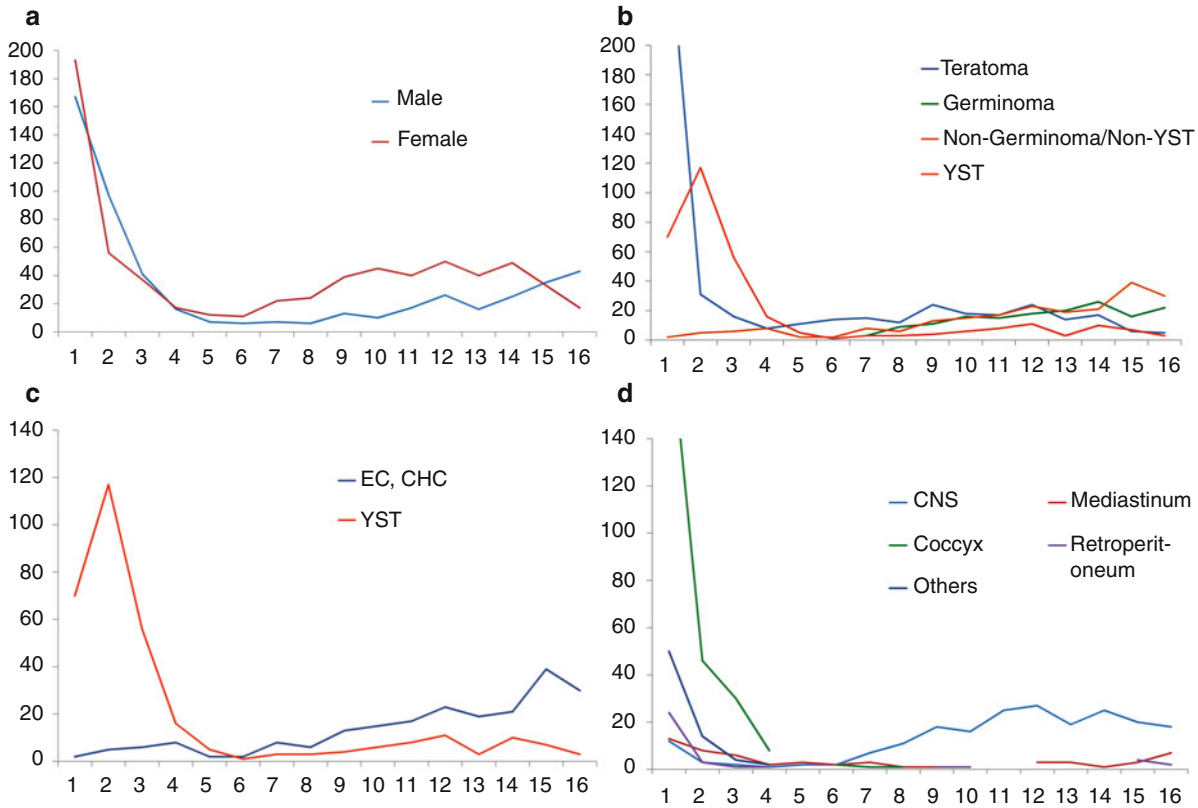


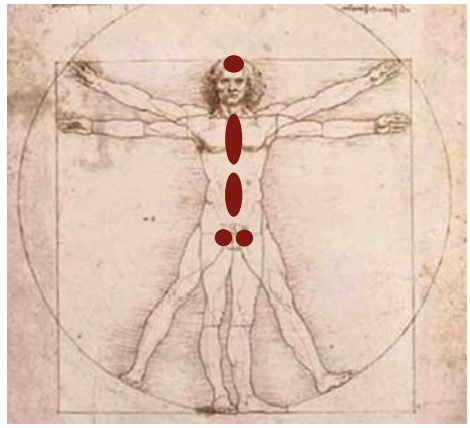
Fig. 39.1.1 (**a**) Age distribution of germ cell tumors by age and sex. (**b**) Age distribution of germ cell tumors by histology – teratomas. (**c**) Age distribution of germ cell tumors by histology – nongerminomatous. (**d**) Age distribution of germ cell tumors by site

Fig. 39.1.1d. This figure illustrates that for some specific tumor sites such as the testis and the mediastinum, a bimodal age distribution can be recognized, with a subgroup occurring during infancy and a separate group developing after the onset of puberty (Schneider et al. 2002a). In contrast, no separate epidemiological groups can be appreciated in CNS and ovarian germ cell tumors, which only show an incidence peak after the onset of puberty. Lastly, some germ cell tumors such as vaginal and sacrococcygeal germ cell tumors only develop during infancy and childhood but not after the onset of puberty (Fig. 39.1.2) (Schneider et al. 2004a).

The survival of children with pediatric germ cell tumors has greatly improved with the application of lessons from adult GCT. For some patients with GCT, a reduction in therapy may be warranted. However, there is still a small population for which more intensive or adaptive therapy is warranted. The paucity of such events suggests that international collaborations and advances in molecular understanding of GCT may be crucial.

39.1.1 Histogenesis and Biology of Extragonadal Germ Cell Tumors

As we investigate molecular differences in GCT from children and adolescents, it should be recognized that few pediatric tumors have been studied (Palmer et al. 2007). When addressing tumor-specific genetic changes, the heterogeneity of the pediatric germ cell tumors is evident also in studies investigating their genetic and molecular properties. Biologically distinct subcategories have been described in the pediatric population (Bussey et al. 1999a; Perlman et al. 2000; Schneider et al. 2006; Palmer et al. 2007).



	<10	>10 years
CNS	10%	35%
Ovary	15%	45%
Testis	25%	10%*
Coccyx	35%	0%
Others	15%	10%

1,442 patients from the MAHO/MAKEI/SIOP CNS GCT registry

*Due to the age cut-off, testicular GCTs during puberty are under-reported to this registry. Last, it should be noted that this figure cites data from Schneider et al. Ped Blood Cancer 2004

Fig. 39.1.2 Distribution of germ cell tumors by site and age

39.1.2 Sex-Chromosomal Abnormalities in Germ Cell Tumors

Sex-chromosomal abnormalities have been associated with the development of germ cell tumors. The most recognized association is the one of ovarian germ cell tumors with Turner syndrome, in particular, in patients with microscopic residues of Y-chromosomal sequences. In these patients, dysgerminomas may develop within gonadoblastomas, which therefore constitutes a precursor lesion of invasive germ cell (Cools et al. 2006). Moreover, testicular feminization and Swyer syndrome, a disorder characterized by a female appearance but with gonadal dysgenesis, i.e., hypoplastic streak gonads in a cytogenetically male patient, are also associated with the development of gonadoblastoma and overt germ cell tumor over time. Therefore, prophylactic oophorectomy is recommended in these patients.

Moreover, some extragonadal germ cell tumors are also associated with sex-chromosomal aberrations. Thus, mediastinal GCT have been associated with Klinefelter's syndrome (47,XXY) (Nicholset al. 1987a). Approximately 50% of adolescents with mediastinal germ cell tumors have cytogenetic changes consistent with Klinefelter's syndrome (Schneider et al. 2002a) (see Chap. 24). In addition, a high frequency of numeric aberrations of sex chromosomes have been demonstrated in germ cell tumors of the central nervous system (Yu et al. 1995).

39.1.3 The Primordial Germ Cell Hypothesis of Extragonadal Germ Cell Tumors

More than 35 years ago, Teilum postulated that all different histologic entities of germ cell tumors develop from an omnipotent primordial germ cell that is capable of differentiation along the germ line and into embryonic and extraembryonic tissues (Teilum et al. 1975a) (Fig. 39.1.3). This so-called holistic concept of the histogenesis of germ cell tumors remains fascinating since it provides a very instructive theory that is able to explain both the apparent heterogeneity of germ cell tumors and the observation of tumors with mixed histology. Moreover, patients who at relapse present with a histology different from that at initial diagnosis can be explained based on this theory. Last, if the holistic concept is considered in the light of the knowledge of primordial germ cell migration during early embryonal development, even the development of seminomatous and nonseminomatous germ cell tumors at extragonadal sites can be explained. However, several aspects still remain elusive. For instance, it is unclear why the histologic differentiation of germ cell tumors is restricted to specific subtypes at specific sites, while it is not at others. At the sacrococcygeal region, teratomas and yolk sac tumors can be found, while vaginal germ cell tumors always present as pure yolk sac tumors. Therefore, it can be assumed that the microenvironment may play a substantial role in modulating tumor development and differentiation.

There has been considerable debate as to whether the heterogeneous germ cell tumors, in particular extragonadal teratomas may originate from midline somatic stem cells. This debate has been fostered by the experimental observation that teratoma like tumors may develop at the injection site of cultured embryonal stem cells (Thomson et al. 1998). Moreover, the development of an isochromosome 12p, the pathognomic marker of germ cell tumors in young men, has been described in long-term culture of embryonal stem cells (Draper et al. 2004).

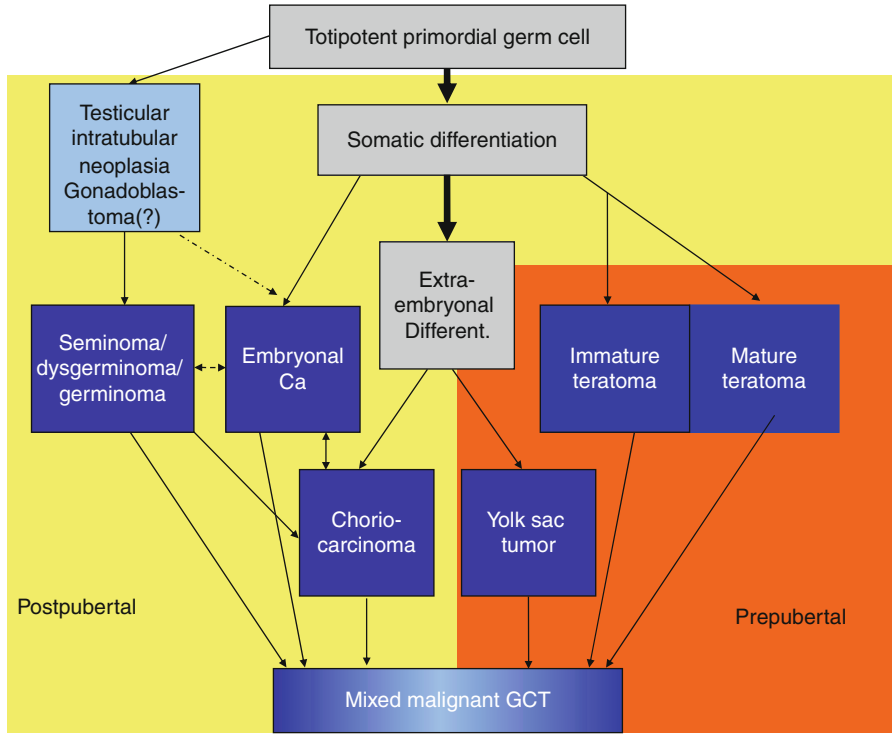


Fig. 39.1.3 Primordial germ cell hypothesis of extragonadal germ cell tumor development

On the other hand, there is molecular evidence that both gonadal and extragonadal germ cell tumors originate from primordial germ cells at different stages of development. Thus, the examination of the epigenetic control of genomic imprinting reveals a methylation pattern that is characteristic of primordial germ cells during and shortly after their migration during early embryonal development (Bussey et al. 1999a; Schneider et al. 2001a). Moreover, the tumors cells retain a specific embryonal stem-cell-like expression pattern, characteristic of primordial germ cells (Hoei-Hansen et al. 2006). However, this hypothesis has recently been challenged by the observation that neural stem cells may also show loss of the methylation imprint, e.g., of SNRPN, making these cells alternative candidates from which CNS germ cell tumors may be derived (Lee et al. 2010). The loss of methylation pattern of other genes such as IGF-2 however distinguishes germ cell tumors from other embryonal tumors with presumed stem cell origin such as nephroblastoma (Sievers et al. 2005a). This observation, as well as modern findings on the role of the microenvironment for the development of extragonadal germ cell tumors, still supports the hypothesis of a specific germ cell origin of these tumors (Oosterhuis et al. 2007).

The primordial germ cells first become evident in the extraembryonic yolk sac by the fourth week of gestation. By the fifth week, the germ cells migrate through the mesentery to the gonadal ridge. This migration appears to be mediated by the c-kit receptor and its ligand, stem-cell factor, or steel factor. Primordial germ cells express c-kit. Stem-cell factor is expressed with an increasing gradient from yolk sac to gonadal ridge, guiding germ cells to the gonadal ridge. In animal models, primordial germ cells not expressing c-kit are unable either to migrate to the gonad or to proliferate during this migration (Godin et al. 1991; Dolci et al. 1993; Orth et al. 1997).

The association of c-kit mutations (codon 816) with bilateral or familial germ cell tumors underlines the importance of this gene during germ cell development (Looijenga et al. 2003; Rapley et al. 2004). In addition, c-kit mutations or c-kit amplifications have also been reported in 27% of unilateral ovarian dysgerminomas (Cheng et al. 2010).

Germ cell migration is also controlled by additional mediators such as the chemokine soluble derived factor 1 (SDF-1) and its receptor CXCR-4 (Doitsidou et al. 2002). Germ cells express CXCR-4 and migration is directed by the expression and secretion of SDF-1 (CXCL-12) in the mesenchyme of the gonadal

Table 39.1.1 Histology and genetics

Group	Histology	Epigenetics	Genetics
GCTs of infancy and childhood	Teratoma Yolk sac tumor	Premeiotic Loss of imprinting	Normal −1p, + 1p, − 6p, + 20
GCTs of adolescence and adulthood	Teratoma Seminoma Mal. nonseminoma	Meiosis I Loss of imprinting	+12p
Spermatocytic seminoma (testis)		Meiosis II Gamet. imprinting	+9
Cystic teratoma (ovary)		Meiosis II Gamet. imprinting	(23,X)×2

ridges. Mice that lack either SDF-1 or CXCR-4 also fail to populate the gonadal ridges and may persist at extragonadal sites. Moreover, aberrant migration of germ cells can be induced by aberrant expression of SDF-1 (Molyneaux et al. 2003). Of note, expression analysis of SDF-1 and CXCR-4 has demonstrated aberrant expression of CXCR-4 in extragonadal germ cell tumors, which typically locate at sites known to express SDF-1 (Gilbert et al. 2009). These data from embryological and tumor genetic studies support the hypothesis that extragonadal germ cell tumors may arise from germ cells that have migrated aberrantly, and in which expression of growth factors aberrantly persists beyond the embryonal period. However, yet unpublished data indicate that no mutations of CXCR-4 can be detected in extragonadal germ cell tumors, thus indicating that aberration of the SDF-1 and CXCR-4 axis is not involved in the development of extragonadal germ cell tumors (D.T.S. unpublished data).

39.1.4 Complex Correlation of Biology, Site, and Histology

It should be noted that apart from the predominance of midline sites and the histologic similarity to the histologic spectrum of gonadal germ cell tumors, there are pronounced biologic and histologic differences between germ cell tumors at different anatomical sites.

Thus, during childhood the histologic appearance of germ cell tumors is almost exclusively restricted to teratoma and yolk sac tumor (Table 39.1.1). Tumors at other sites such as vaginal germ cell tumors only present as yolk sac tumors. Both tumors are not seen during adolescence. After the onset of puberty, mediastinal and central nervous system germ cell tumors predominate among extragonadal germ cell tumors. These tumors present with the whole spectrum of adult germ cell tumors, including seminomas, nonseminomas, and teratomas. Of note, mediastinal germ cell tumors may present with both patterns, one consisting of teratomas and yolk sac tumors during childhood and one with seminomas, nonseminomas, and teratomas during adolescence. These two groups are distinguished by different genetic profiles, both corresponding to the genetic aberrations seen in germ cell tumors at other anatomical sites during the corresponding age group (Schneider et al. 2002a).

Thus, genetic studies have substantially helped in categorizing the different distinct clinical entities of germ cell tumors and in defining childhood germ cell tumors at a distinct site, despite their heterogeneous clinical presentation at different anatomical sites. Genetic studies have also provided information regarding the pathogenesis of pediatric germ cell tumors including information on constitutional genetic changes that may lead to increased susceptibility and tumor-specific genetic changes. However, little is still known regarding the former, particularly with regard to infantile germ cell tumors. Nevertheless, it has become clear that with the onset of puberty, the spectrum of genetic changes is seen in germ cell tumors, and therefore the biology changes.

39.1.5 Genetics of Prepubertal Germ Cell Tumors

In children younger than 10 years, germ cell tumors arising in gonadal and extragonadal sites are similar in clinical presentation, histology, and genetics (Table 39.1.2). Most teratomas in this age group are diploid, have normal karyotypes, and, if completely resected, behave in a

Table 39.1.2 Histology and markers

Histology	AFP	β-HCG	Immunohisto-marker	Prepubertal	Postpubertal
Teratoma, mature	–	–	–	+	+
Teratoma, immature	(+)	–	–	+	+
Teratoma with mal. Transformation, e.g., carcinoma	(+)	–	–	–	+
Germinoma (syn. seminoma, dysgerminoma)	–	(+)	OCT3/4, c-kit	–	+
Embryonal Carcinoma	–	–	CD30 OCT3/4	–	+
Choriocarcinoma	–	+++	β-HCG	(+)	+
Yolk sac tumor	+++	–	AFP CD34	+	+
Mixed malignant GCT	–/+	–/+	As above	TER + YST	All comb.
Gonadoblastoma	–	–	OCT3/4	–	+
Polyembryoma	–	–	–	–	–

benign fashion regardless of degree of immaturity and site of origin (Kaplan et al. 1979a; Silver et al. 1994; Bussey et al. 1999a; Schneider et al. 2001b, c; Harms et al. 2006a). Malignant germ cell tumors in these young children are almost exclusively yolk sac tumors, may arise from a preexisting teratoma, and most often are diploid or tetraploid (Perlman et al. 1994a; Silver et al. 1994; Bussey et al. 1999a). Recurrent cytogenetic abnormalities involve chromosomes 1, 6, and 20 among others, but only rarely the 12p (Bussey et al. 1999a; Perlman et al. 1994a, 2000; Mostert et al. 2000; Schneider et al. 2001b, c, 2006; Palmer et al. 2007).

In situ hybridization and loss of heterozygosity studies have demonstrated deletion of 1p36 in 80–100% of infantile malignant germ cell tumors arising from testicular and extragonadal sites (Jenderny et al. 1995; Bussey et al. 2001; (Zahn et al. 2006; Perlman et al. 1996). Genetic surveys of regions of gain or loss in these infantile yolk sac tumors document recurrent loss of 6q24-qter, gain of 20q and 1q, and loss of 1p. A small number of tumors show evidence for c-myc or n-myc amplification (Schneider et al. 2002a, Germ Cell Tumours V, 127–128). The clinical significance for these markers is however entirely unknown.

Recently, first expression studies of mRNAs and micro-RNAs in childhood germ cell tumors have been reported (Palmer et al. 2008, 2010). Germ cell tumors show recurrent mRNA and micro-RNA profiles that segregate tumors primarily according to histology. Furthermore, expression profiles distinguished between childhood and adult germ cell tumors. Of note, within a distinct histology, the yolk sac tumor, tumors had different expression profiles for different ages. In contrast, no site-specific differences were reported within a given histology and age group. Gene expression studies have also yielded insights into the molecular biology of childhood germ cell tumors. Thus, in pediatric yolk sac tumors, genes associated with activation of the canonical WNT pathway were expressed at high levels (Fritsch et al. 2006; Palmer et al. 2008). Additional studies have shown that this pattern is associated primarily with epigenetic dysregulation of WNT control genes among others, the adenomatosis poliposis gene and cell surface regulators of *wnt* signaling (unpublished data).

Figures 39.1.4 and 39.1.5 demonstrate a summary of CGH profiles of 116 malignant germ cell tumors and 32 pure teratomas, respectively. The results are separated by age, demonstrating frequent chromosomal imbalances of chromosomes 1p, 6q, and 20q in prepubertal tumors, irrespective of tumor site. Postpubertal tumors show recurrent gain of 12p and other less recurrent imbalances. Of note, all pure teratomas prior to puberty are balanced, while postpubertal teratomas may show recurrent imbalances, resembling a pattern seen in malignant germ cell tumors of the same age group. However, the number of chromosomal imbalances is smaller than in corresponding malignant tumors.

Fig. 39.1.4 CGH profiles of 116 malignant germ cell tumors (Schneider et al. 2006)

In conclusion, tumors in children younger than10 years of age are biologically distinct from those tumors that develop in adolescents and adults. This is true, even if the histology, e.g., yolk sac tumor, is microscopically undistinguishable.

39.1.6 Genetics of Postpubertal Germ Cell Tumors

Testicular germ cell tumors of the young adult constitute the best studied entity of germ cell tumors. These tumors appear to arise from a precursor lesion, which is histologically defined as testicular intratubular neoplasia (TIN). TIN may grow within the seminiferous tubules. Tumor cells express specific transcription factors such as c-kit and OCT3/4, indicating their origin from immature pluripotent gonocytes (Oosterhuis and Looijenga 2005a). Obviously, the progression of TIN to invasive germ cell cancer is associated with the development of additional cytogenetic events, including aberrations of chromosome 12p. Bilateral testicular (2–5%) and familial (2%) cases have been reported.

The isochromosome 12p constitutes the biologic hallmark of testicular and extragonadal germ cell tumors in adults (Atkin and Baker 1982; Rodriguez et al. 1992). It is formed by centromeric fusion of two short arms of chromosome 12, with loss of the long

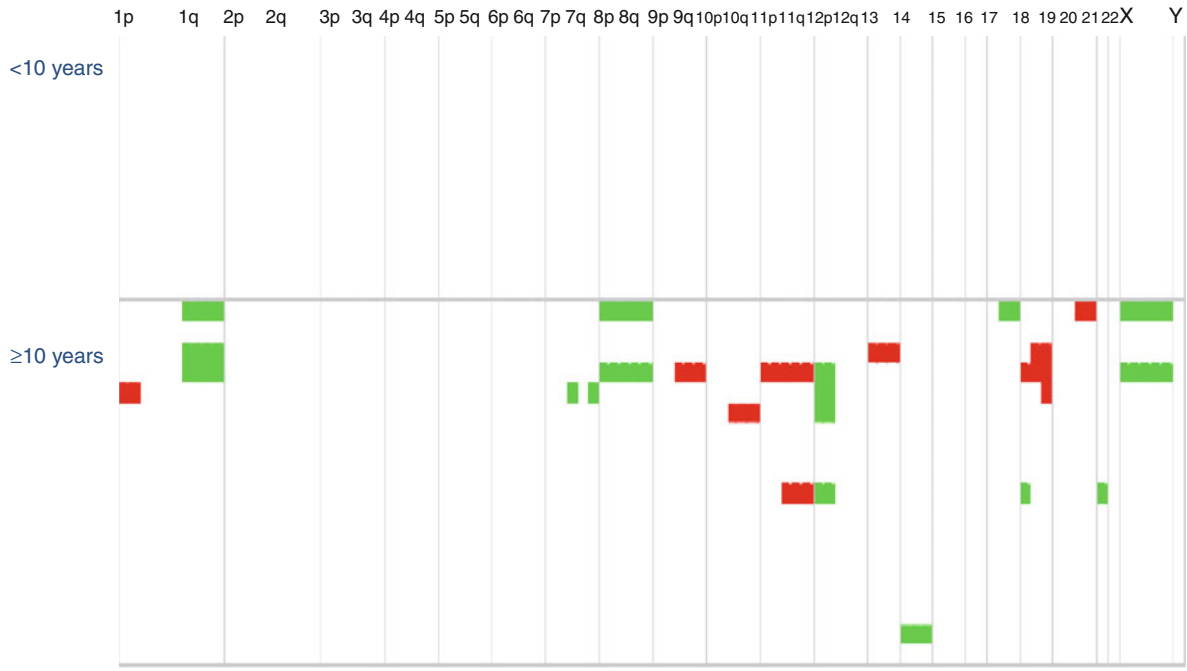


Fig. 39.1.5 CGH profiles of pure teratomas (Schneider et al. 2006)

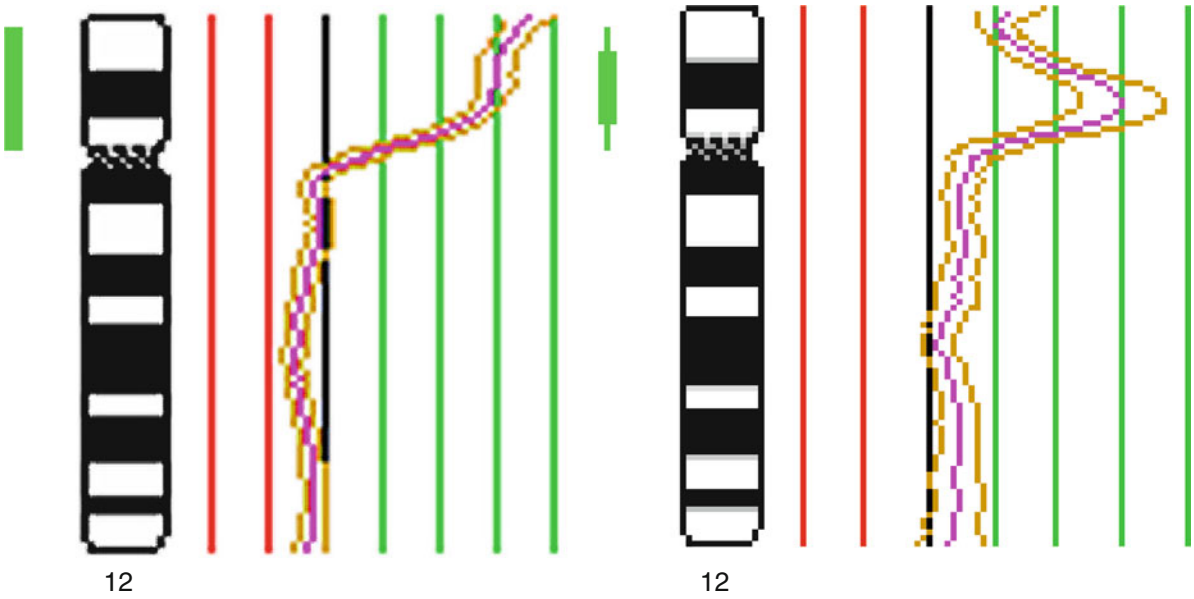


Fig. 39.1.6 CGH of CNS germ cell tumor with amplification at 12p22 (isochromosome 12p)

arms. The isochromosome 12p can be detected in approximately 80% of adult malignant germ cell tumors. In addition, in adults, even pure teratomas may display 12p aberrations. In those cases with no isochromosome 12p, amplification of 12p chromosomal material can be detected with molecular techniques such as fluorescence in situ hybridization or comparative genomic hybridization (Samaniego et al. 1990; Schneider et al. 2006). Figure 39.1.6 demonstrates a comparative genomic hybridization of a central nervous

system germ cell tumor with an amplicon at 12p22. The region from 12p11 to 12p12 has been defined as the region most commonly involved in amplification. Chromosomal amplification is cytogenetically recognizable as double minutes or homogeneously staining region, e.g., on marker chromosomes. In this chromosomal region, several candidate oncogenes such as *KRAS* and cyclin D2 are located. However, their etiopathogenetic role remains unclear. In addition, this region harbors stem cell genes such as *STELLAR* and *NANOG* (Oosterhuis and Looijenga 2005a).

The development of adult testicular germ cell tumors is associated with cryptorchidism and testicular dysgenesis, leaving a proportion of patients infertile (Skakkebaek et al. 2003; Skakkebaek 2004). In the context of a testicular dysgenesis syndrome, TIN and invasive germ cell tumors may be detected "accidentally" during medical evaluation of infertility. For general pediatricians and pediatric surgeons, question arises whether medical or surgical treatment of cryptorchidism may influence the risk of germ cell tumor development in the cryptorchid testis. The lifetime risk of later development of germ cell tumors in cryptorchid children is estimated to 2–18% (Buetow 1995). In this context, the biologic association between cryptorchidism and germ cell tumor is still elusive. It remains unclear if the risk of later germ cell tumor development can be reduced by early orchidopexy (and at what age) or whether it is inherent to an underlying testicular dysgenesis and maturation disorder.

While ovarian germ cell tumors are associated with testicular feminization, constitutional loss of one X chromosome, and presence of aberrant Y chromosomal genetic material, no such association has been reported in girls with extragonadal germ cell tumors. However, mediastinal germ cell tumors are associated with constitutional Klinefelter's syndrome (Nichols et al. 1987a). Compared to patients with normal constitutional karyotype, these tumors tend to occur at a younger age and predominantly with malignant nonseminomatous histology. Of note, the risk of germ cell tumors at other anatomical sites including the testis does not appear to be significantly increased in Klinefelter's syndrome (Hasle et al. 1995), although some single patients with CNS germ cell tumors and Klinefelter's syndrome have been reported (Prall et al. 1995).

The two most common sites for extragonadal germ cell tumors in adolescents and adults are mediastinum and brain. Cytogenetic analysis of central nervous system teratoma has shown a high frequency of sex-chromosome abnormalities, most commonly increased copies of the X chromosome (Yu et al. 1995). The i (12p) has been described in some, but not all, pineal germinomas, but it has not been seen in pineal teratoma (Schneider et al. 2006). Ploidy analyses of mediastinal germ cell tumors suggest that most are diploid or tetraploid (Oosterhuis et al. 1990), and those that are malignant contain the i (12p) and the other genetic changes seen in adolescent testicular germ cell tumors (Dal Cin et al. 1989; Schneider et al. 2002a). The extragonadal germ cell tumors (almost exclusively, nonseminomatous mediastinal tumors) in adolescents and adults are associated with hematopoietic malignancies of various cell lineages that present soon after the initial presentation of the germ cell tumors. The most common presentation is acute megakaryocytic leukemia, and the malignant hematopoietic clone commonly demonstrates i (12p).This differs from hematopoietic malignancies that arise secondary to therapy (Chaganti et al. 1994; Hartmann et al. 2000).

39.1.6.1 Pathology

Germ cell tumors comprise numerous histologic subtypes; however, the microscopic morphology of a distinct histologic subentity is undistinguishable regardless of age at diagnosis, tumor site, and genetic background (Hawkins and Perlman 1996a). Thus, tissue from ovarian cystic teratoma, a tumor arising from premeiotic cells, is undistinguishable from mature cystic teratoma of the sacrococcygeal region or the CNS.

Currently, germ cell tumors are most commonly classified according to the World Health Organization revised classification for testicular, ovarian, and central nervous system tumors. Still, there are some inconsistencies in the site-specific classification, in that different terms are used for histologically and biologically identical tumors, i.e., seminomas of the testis, dysgerminomas of the ovary, and germinoma of the CNS. These inconsistencies are mainly explained by the historical development of the site-specific classifications. However, in all classification systems, the approach to mixed malignant germ cell tumors composed of different histologic components is comparable. Thus, it is highly recommended that all different histologic entities present in each single tumor should be listed separately so that a specific

Table 39.1.3 Pediatric germ cell tumor – histology

- Teratoma
  - Mature teratoma
  - Immature teratoma (grades 1–3)
- Germinoma (seminoma and dysgerminoma)
- Embryonal carcinoma
- Choriocarcinoma
- Polyembryoma
- Mixed malignant germ cell tumor
  - Teratoma or immature teratoma with malignant GCT elements
  - Teratoma with other malignant elements (e.g., squamous cell carcinoma)

description is provided that may assist in the optimal planning of the multimodal therapy. For instance, in a mixed malignant germ cell tumor with germinoma and teratoma, a 2-cm tumor residue after chemotherapy should be interpreted differently from a 2-cm residue of a pure germinoma; the first could represent residual teratoma requiring resection, whereas a residue of pure germinoma may be pure scar to be followed only.

The histologic classification of these tumors is shown in Table 39.1.3. The pathologic features of each histologic subtype are discussed separately.

39.1.6.2 Mature Teratoma

Teratomas are the most common histologic subtype of childhood germ cell tumors (Dehner 1983a; Harms and Janig 1986; Hawkins 1990; Young and Scully 1990a). They can arise in the gonads and virtually all extragonadal locations. In fact, sacrococcygeal teratoma constitutes the most common tumor in neonates. Mature teratomas of the gonads are encapsulated and present as multicystic or solid tumors. Extragonadal teratomas differ from their gonadal counterparts in that they commonly lack a clearly defined external capsule, which interferes with surgical preparation and hence complete tumor resection. In sacrococcygeal teratoma, this characteristic requires the coccyx to be removed during surgery to reduce the risk of recurrence (Göbel et al. 1997a, 1998a). A simple enucleation of a mature teratoma may be possible in skilled surgical hands.

The mature teratoma is composed of mature representative tissues from one or up to all three germ cell layers: ectoderm, mesoderm, and endoderm (Fig. 39.1.7a). Although any tissue type may be seen, the most commonly found are skin and skin appendages, adipose tissue, mature brain, intestinal epithelium, and cystic structures lined by squamous, cuboidal, or flattened epithelium. Some tissue types are site-specific. For example, hematopoietic, pancreatic, or pituitary tissue frequently is found in mediastinal tumors and rarely in teratoma at other sites. Components of the mature teratoma occasionally may be biologically active, with secretion of enzymes or hormones, including insulin, growth hormone, prolactin, and vasopressin.

39.1.6.3 Immature Teratoma

Pediatric immature teratomas primarily occur in extragonadal sites in children and in the ovaries of girls near puberty (Göbel et al. 1998a; Marina et al. 1999a). Immature teratomas have a gross appearance similar to mature teratoma and are composed of representative tissues from all three germ layers. Unique to these tumors is the presence of various immature tissues, usually neuroepithelium, although immature ectodermal, mesodermal, and endodermal elements also may be observed (Fig. 39.1.7b). A number of grading systems have been established for immature teratoma, all of which are variations of the system originally devised by Thurlbeck and Scully (1960). All currently used grading systems, such as the one proposed by Gonzalez-Crussi (Gonzalez-Crussi et al. 1978), quantify the degree of immaturity in the lesion. Grade 0 contains only mature tissue, while grade 3 contains more than 3 areas of immature tissue per low power slide. This grading system to pediatric germ cell tumors has not consistently been applied. Only, within the German MAKEI studies, a consistent reference pathologic evaluation of mature and immature teratomas has been implemented, allowing for evaluating the clinical impact of immaturity and the detection of microfoci of yolk sac tumor within teratomas.

The prognostic impact of grading of immature elements in childhood immature teratoma is not clear. High immaturity itself does not confer a poor prognosis if the tumor is completely resected. However, the risk of incomplete resection is obviously higher in very immature teratomas that tend to show more infiltrative growth in the absence of a clearly distinguished tumor capsule (Göbel et al. 1997a, 1998a).

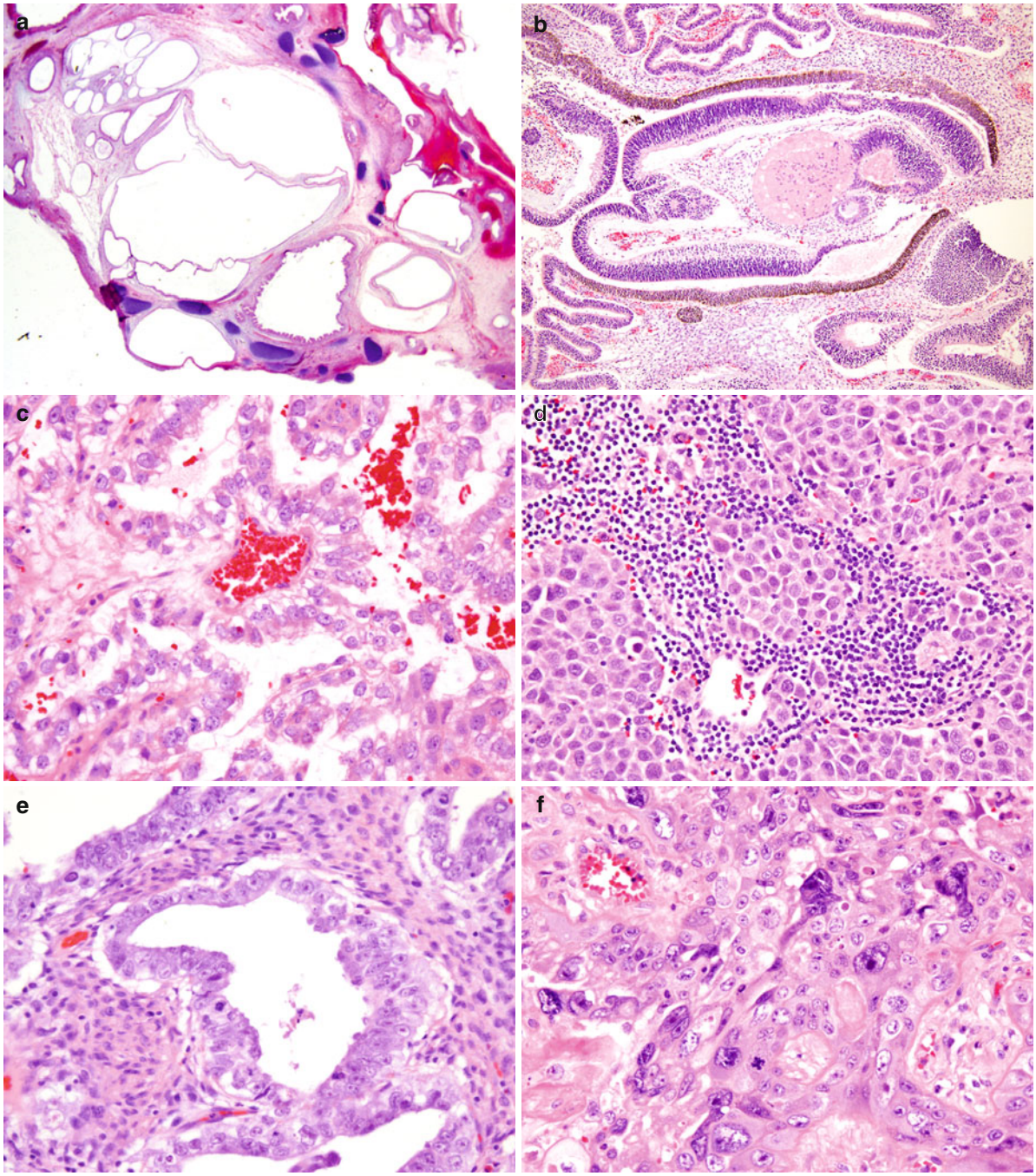


Fig. 39.1.7 (**a**) Teratoma – encapsulated cystic structure with ectoderm, mesoderm, and endoderm. In this area, cartilage and skin tissue is apparent. (**b**) Immature teratoma – myxoid background with large areas of immature neuroepithelium. (**c**) Yolk sac tumor showing Schiller-Duval body with central blood vessel surrounded by tumor cells and a space before next layer of tumor cells. (**d**) Germinoma showing monomorphic cells with abundant clear cytoplasm surrounded by lymphocytic infiltrate. (**e**) Embryonal carcinoma showing large overlapping nuclei with eosinophilic cytoplasm. (**f**) Choriocarcinoma showing small cells associated with large giant syncytiotrophoblasts

Immature teratomas in children behave in a malignant fashion only if foci of malignant germ cell elements (usually yolk sac tumor) are present, and if they are resected incompletely. Clusters of yolk sac tumor can be easily overlooked because they may be very small. Since these may not stain for AFP by immunohistochemistry, the experience of the pathologist is of crucial importance. Tumors containing such foci likely are responsible for the reports that immature teratoma may metastasize. Surgical resection is not always possible, and in some cases, a "benign" immature teratoma proves fatal.

39.1.6.4 Yolk Sac Tumor

Yolk sac tumors are the most common pure malignant GCT in young children (Young and Scully 1990a). Apart from very few exceptions, it is the only malignant GCT type occurring during infancy. Yolk sac tumors rarely occur in pure form in adolescents but more frequently are a component of the mixed malignant germ cell tumors occurring in these locations. Grossly, these tumors consist of friable, pale-gray, mucoid tissue with variable amounts of hemorrhage and necrosis. The microscopic features are also wide and have been characterized fully only in the last two decades. Four general patterns and a number of variations have been recognized. These patterns are useful in the recognition of yolk sac tumor, but their clinical relevance is currently unknown.

The pseudopapillary or festoon pattern and the microcystic or reticular patterns are the most common and widely recognized. Both contain Schiller-Duval bodies (Fig. 39.1.7c). The microcystic or reticular pattern is associated most often with eosinophilic globules and strands that only occasionally stain positively for AFP or α_1-antitrypsin. The pseudopapillary and parietal patterns often are observed after chemotherapy (Ulbright et al. 1990). The solid pattern usually is found only focally and may mimic embryonal carcinoma. A variant of the solid pattern is the hepatoid pattern, which closely resembles fetal liver (Nakashima et al. 1987). A fourth pattern is the polyvesicular vitelline pattern, characterized by small, empty cystic structures lined by a single layer of malignant cells that merge from cuboidal to flat. The cells often are embedded in a loose, frequently myxoid stroma. Two other patterns have been described. The enteric pattern resembles the fetal human gastrointestinal tract and typically stains positively for AFP and chorionic embryonic antigen (Clement et al. 1987; Cohen et al. 1987; Ulbright and Roth 1987). The mesenchyme-like pattern stains positively for cytokeratin and vimentin but not for AFP and has been implicated as the source of the sarcomas that occasionally occur in patients who have had a yolk sac tumor (Nakashima et al. 1987).

In general, AFP is the characteristic immunohistochemical (and clinical) marker of yolk sac tumors. Remarkably, it may not consistently stain all tumor cells but may rather show a spotty staining pattern, so that a negative AFP staining of yolk sac tumor microfoci may not exclude the presence of yolk sac tumor. Therefore, the measurement of AFP in the serum (and cerebrospinal fluid in case of a CNS tumor) is complementary to immunohistochemistry.

39.1.6.5 Germinoma

Germinomas, also termed dysgerminomas (ovary) or seminomas (testis), are the most common pure malignant germ cell tumors that occur in the ovary and central nervous system in adolescents (Talerman 1987; Ho and Liu 1992). Pure seminomas are unusual in men younger than 20 years and rarely occur prior to the onset of puberty. The exception is in patients with sex-chromosomal abnormalities or cryptorchidism, where tumors often present at an earlier age.

On gross pathology, germinomas are encapsulated, solid, gray-pink tumors with a rubbery consistency and occasional small foci of hemorrhage and necrosis (Fig. 39.1.7d). Microscopically, the tumor cells are arranged in nests separated by bands of fibrous tissue in which variable numbers of lymphocytes are identified. The cells are large, with clear cytoplasm, distinct cell membranes, and large round nuclei having one or two prominent nucleoli. Granulomas with giant cells frequently are present.

Syncytiotrophoblasts also may be present, but they do not alter the prognosis of the tumor unless they are associated with cytotrophoblasts in foci of choriocarcinoma. These tumors are then termed mixed malignant germ cell tumors. Immunohistochemically, the germinoma cells have strong staining for the stem cell marker OCT3/4, placental alkaline phosphatase (PLAP), and c-kit, whereas the syncytiotrophoblasts may stain for human chorionic gonadotropin beta-subunit (β-HCG). In such tumors, a slight elevation of β-HCG may be found in the serum or the cerebrospinal fluid ion case of CNS tumors.

39.1.6.6 Embryonal Carcinoma

Embryonal carcinoma rarely occurs in a pure form in children and is more often a component of a mixed malignant GCT of adolescents (Young and Scully 1990a; Hawkins and Perlman 1996a). This component is commonly seen in adult testicular GCT. They are characterized by large cells with large, overlapping nuclei and very large, round nucleoli. The major pattern is epithelial and consists of large nests of cells with varying amounts of central necrosis (Fig. 39.1.7e). Pseudotubular and papillary patterns that may be confused with those of yolk sac tumor are frequent, but the cells are AFP-negative, and the tumors typically lack the eosinophilic hyaline globules characteristic of yolk sac tumors. Unlike other germ cell tumors, embryonal carcinoma is consistently positive for CD30 by immunohistochemical staining. In addition, they stain positive for OCT3/4 (Looijenga et al. 2003).

39.1.6.7 Choriocarcinoma

Choriocarcinoma rarely occurs outside the context of malignant mixed germ cell tumors in adolescents (Young and Scully 1990a; Hawkins and Perlman 1996a). The rare case of pure choriocarcinoma detected in infants almost always represents metastasis from maternal or placental gestational trophoblastic primary tumor (Belchis et al. 1993). These tumors characteristically are very hemorrhagic and friable. Microscopically, two types of cells must be present to confirm the diagnosis: cytotrophoblasts, which classically appear as closely packed nests of relatively uniform, medium-sized cells having clear cytoplasm, distinct cell margins, and vesicular nuclei, and syncytiotrophoblasts, which represent multinucleate syncytial trophoblastic cells (Fig. 39.1.7f). The syncytiotrophoblastic elements stain positively for β-HCG, accounting for the associated high concentrations of serum β-HCG in these patients. If choriocarcinoma arises in the CNS, β-HCG may be detected both in the cerebrospinal fluid and the serum, sometimes with discrepant findings in the two compartments. Clinically, choriocarcinoma is associated with widespread hematogenic metastases including CNS metastases, which may be complicated by CNS hemorrhage.

39.1.7 Serum Tumor Markers

Due to their crucial importance for the categorization of childhood germ cell tumors, the serological markers α_1-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are discussed in detail. AFP, an α_1-globulin, is the earliest and predominant serum-binding protein in the fetus, reaching its peak concentration at 12–14 weeks' gestation and gradually falling to reach an adult normal level of less than 10 ng per dL at approximately age 1 year (Gitlin et al. 1972) (Table 39.1.4). In some patients, adult AFP normal serum levels of AFP are reached only at the end of the second year of life (Blohm et al. 1998a). As AFP levels begin to decline in fetal development, albumin becomes the principal serum-binding protein. In early embryogenesis, AFP is produced in the yolk sac and later by hepatocytes and the gastrointestinal tract. Since AFP may cross the placenta, AFP of pregnant mothers may be significantly elevated.

Table 39.1.4 Serum AFP levels in first year of life for preterm and term infants

Age	Preterm (<37 weeks)	Term
Birth	31,261–799,834	9,120–190,546
1 week	6,039–311,889	1,480–58,887
1 month	389–79,433	16–1,995
3–4 months	9–18,620	3–417
6–24 months	0–372	0.8–87

Adapted from report by Blohm et al. (1998)
AFP levels (ng/ml) reported as 95.5% intervals

In 1974, the association between serum elevation of AFP and the natural history of adult germ cell tumors was described. Elevated serum levels or positive immunohistochemical staining of germ cell tumors for AFP indicates the presence of malignant components, specifically yolk sac or embryonal carcinoma (Table 39.1.2). The serum half-life ($t_{1/2}$) of AFP is 5–7 days, but may be longer in particular at lower levels, e.g., during the second half of the first year of life (Blohm et al. 1998a). Because of the wide variation in levels at birth, especially with infants of less than 40 weeks' gestational age, and the wide variability in $t_{1/2}$ at different ages within the first year of life, difficulties arise in interpreting decay of serum AFP as an indication of residual or recurrent GCT in infants younger than 12 months (Blohm et al. 1998a; Schneider et al. 2001a).

Increasing levels of serum AFP, however, are not necessarily indicative of tumor progression. Abrupt escalation in serum AFP can occur after chemotherapy-induced tumor lysis. Spurious persistence of elevated serum AFP may reflect an alteration in hepatic

function from such conditions as viral hepatitis (hepatitis B, hepatitis C, and human immunodeficiency virus–associated hepatitis), cholestasis secondary to anesthesia, metabolic disease (e.g., tyrosinemia type I) or exposure to phenytoin or methotrexate. Other neoplastic conditions associated with elevated serum AFP include hepatoblastoma, hepatocellular carcinoma, pancreaticoblastoma, and pancreatic, gastrointestinal, or bronchial adenocarcinomas. AFP is not only helpful in detecting significant yolk sac tumor components but may also assist in prognostic assessment. During and after treatment, an elevation in AFP identifies progression or recurrence before tumor can be identified by imaging. In a large cooperative analysis of adult germ cell tumors, high AFP and/or β-HCG levels indicated poor prognosis (Group 1997a). In the British childhood cancer studies, high AFP levels above 1,000 μg/L were associated with unfavorable outcome (Mann et al. 1989a; Mann et al. 2000a). Furthermore, an inadequate decline of AFP that does not follow its half time of 5–7 days indicates pure response to chemo or tumor progression after tumor resection (Schneider et al. 2005a).

Human chorionic gonadotropin (HCG) is a glycoprotein comprised of α- and β-peptide subunits and normally is synthesized during pregnancy by syncytiotrophoblasts of the placenta to maintain viability of the corpus luteum. The α-subunit is similar to α-peptides of other hormones, such as luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone. The β-subunit is antigenically distinct, serving as the basis for the method of serum assay. Minute amounts, less than 5 mIU per mL, are detected in serum of healthy adults; serum $t_{1/2}$ of β-HCG is 24–36 h.

The most frequent for significant rise of β-HCG is pregnancy. Therefore, in case of suspected GCT and elevated β-HCG, pregnancy must be excluded with other techniques, e.g., ultrasound.

Elevation of serum β-HCG in patients with germ cell tumors implies the presence of clones of syncytiotrophoblasts, such as choriocarcinoma, or of syncytiotrophoblastic giant cells, found frequently in germinomas (pure seminomas or dysgerminomas) and occasionally in adult embryonal carcinoma.

Like serum AFP, sudden elevation of serum β-HCG occurs after cell lysis secondary to chemotherapy (Vogelzang et al. 1982). Iatrogenic hypogonadism secondary to bilateral orchiectomy, oophorectomy, or chemotherapy also may be associated with rising levels of serum β-HCG because of an increase in luteinizing hormone that results in immunologic cross-reactivity. Other conditions in which modest elevations of serum β-HCG have been reported include multiple myeloma and other malignancies of liver, pancreas, gastrointestinal tract, breast, lung, and bladder. Simultaneous elevation of serum AFP and β-HCG has been described in ovarian embryonal carcinoma in an 11-year-old and in patients with polyembryoma.

39.1.7.1 Other Markers

Because some germ cell tumors with identifiable malignant elements do not produce measurable amounts of serum AFP or β-HCG, other markers with potential prognostic value have been investigated. Serum LDH, a glycolytic enzyme that appears to correlate with growth and regression of various solid neoplasms, has not shown specificity for a specific histologic subtype of germ cell tumors. In patients with dysgerminoma, serum levels of the LDH isoenzyme 1, the gene which resides on 12p, correlate with the tumor burden and aid in the planning and assessment of surgical management (Schwartz and Morris 1988). Elevated serum LDH levels have not been prognostic in germ cell tumors of prepubertal children.

Human placenta like alkaline phosphatase (PLAP) is a fetal isoenzyme of alkaline phosphatase that is elevated in the sera of up to 30% of patients with stage I disease and of almost 100% of cases with advanced seminoma (Koshida et al. 1991). As with AFP and β-HCG, immunohistochemical staining for PLAP sometimes is useful in determining the origin of histologically undifferentiated tumors.

Although elevated serum levels of carcinoembryonic antigen (CEA) are reported in patients with ovarian tumors, the usefulness of this antigen has been hampered by lack of tumor specificity and correlation to disease natural history.

The carbohydrate antigen CA-125, which is related to the tissues of the coelomic epithelium and müllerian ducts, has been assessed in ovarian cancers of germ cell and epithelial origin. CA-125 has been reported to have some correlation with other tumor markers and to be of value in monitoring patients with ovarian tumors of germ cell, epithelial, and stromal origin (Altaras et al. 1986), although its utility in these patients remains to be defined because of the limited numbers of patients studied to date.

Table 39.1.5 Sensitivity to treatment

	Histologic grading	Sensitivity to chemo	Sensitivity to radiation
Seminoma/ germinoma	Malignant	+++	>24 Gy
Embryonal carcinoma	Malignant	+++	>45 Gy
Yolk sac tumor	Malignant	+++	>45 Gy
Choriocarcinoma	Malignant	+++	>45 Gy
Teratoma, mature/ immature	Benign/ potential for malignant development	?	?

39.1.8 Treatment Overview

The treatment of benign and malignant germ cell tumors requires a coordinated multimodality approach. The strategy is chosen based on data on site, staging, biology, histology, and marker levels (Table 39.1.5). The development of effective chemotherapy regimens has allowed a more adaptive surgical approach that is specific to anatomic site of germ cell tumors. These specifics will be discussed in sections that follow on testicular, ovarian, and extragonadal germ cell tumors. A few guiding principles can be outlined.

39.1.9 Surgical Treatment of Germ Cell Tumors in the Context of Multimodal Therapy

Surgery is a mainstay in the treatment of germ cell tumors. Complete surgical resection is the standard treatment for benign tumors, such as teratomas. There is no evidence that chemotherapy has any significant therapeutic effects in pure teratoma (Göbel et al. 1998a; Marina et al. 1999a). The complete surgical removal of malignant lesions is indicated, if possible. However, the surgical approach to malignant germ cell tumors may be influenced by effective neoadjuvant chemotherapy. In this situation, biopsy may be appropriate.

It must be emphasized that surgical recommendations may differ significantly for children and adolescents and for gonadal and extragonadal germ cell tumors. In general, gonadal tumors are more assessable to complete tumor resection, since most present with a clearly defined tumor capsule often in combination with the organ capsule of the gonad. Therefore, most gonadal tumors are resected completely and the local relapse rate is low. In contrast, extragonadal tumors more often show infiltrating growth and a poorly defined pseudocapsule. These tumors present with considerable size and often develop in anatomically problematic regions such as the brain, mediastinum, or the pelvic floor. Therefore, complete resection with free margins of extragonadal germ cell tumors is often impossible. In this situation, neoadjuvant chemotherapy may substantially facilitate complete resection on delayed surgery.

Malignant germ cell tumors may respond dramatically to neoadjuvant chemotherapy, allowing a less aggressive surgical approach at specific sites such as vaginal yolk sac tumors (Mauz-Körholz et al. 2000). Therefore, resection should not be undertaken to the point of sacrificing vital structures. Chemotherapy may allow a patient to be spared mutilating surgery. In many large extragonadal malignant germ cell tumors, neoadjuvant chemotherapy may increase the chance of complete resection. Eventual complete resection (post-chemotherapy) is the goal if cure of an extragonadal germ cell tumor is to be achieved (Schneider et al. 2000a; Göbel et al. 2001a). Stable radiologic disease with marker normalization may not suggest resistant disease.

The question "is a biopsy needed prior to neoadjuvant chemotherapy?" is approached differently by various groups. Most physicians are more comfortable treating with chemotherapy when a pathologic diagnosis is confirmed. In addition, material for molecular studies of germ cell tumor may be crucial to future treatments. However, it may be in the patient's interest not to biopsy, for example, in the presence of respiratory distress due to mediastinal disease. This strategy must be reserved for secreting tumors. Surgery also plays a significant role in relapsed germ cell tumors.

39.1.9.1 Radiotherapy

Radiotherapy has been used to effectively treat germ cell tumors of germinomatous origin including germinoma (CNS), seminoma (testis), and dysgerminoma (ovarian). Radiation sensitivity correlates with histology (Table 39.1.5). However, the role of radiation in seminoma and dysgerminoma has been reduced by the advent of platinum-based chemotherapy. Nevertheless, radiation therapy, applied as craniospinal irradiation, remains standard treatment for CNS germinoma. However, currently new strategies have been developed

that combine chemotherapy with irradiation to reduced fields and with reduced doses, in order to reduce the risk of long-term radiotherapy-associated sequelae. Radiation therapy may also play a role in the treatment of recurrent germ cell tumors, in particular, if tumors still cannot be resected completely after up-front salvage chemotherapy.

39.1.10 Chemotherapy

The prognosis of germ cell tumors has improved significantly with the development of cisplatin-based therapy in adult testicular GCT patients (DFS 68–92%) (Einhorn and Donohue 1977a; Logothetis et al. 1985; Bosl et al. 1988; Einhorn et al. 1989a). Prior to this effective chemotherapy, children with extracranial malignant germ cell tumors had 3-year survival rates of 15–20% with surgery and radiation therapy (Kurman and Norris 1976a; Billmire and Grosfeld 1986). However, boys with localized testicular tumors did well with surgical resection (Hawkins et al. 1986). Prognosis and appropriate treatment depend on factors such as histology (e.g., seminomatous vs. nonseminomatous), age (young children vs. adolescents), stage of disease, and primary site (Baranzelli et al. 1999a; Marina et al. 2006a). Cisplatin-based chemotherapy has dramatically improved the outcome for children with extracranial GCT, with 5-year overall survival rates of more than 90% (Mann et al. 2000a; Göbel et al. 2001a; Cushing et al. 2004a; Rogers et al. 2004a). Table 39.1.6 describes successful regimens developed by various national pediatric groups. In general, the clinical outcome is comparable with the different protocols; however, the toxicity profile may vary. To develop an optimal consensus treatment strategy, an international meta-analysis would be beneficial. However, such a project is still problematic due to several issues such as different staging systems, different histopathologic classification systems, as well as considerable differences in risk stratification.

In general, substantial reduction of cumulative chemotherapy has become possible with the optimization of multimodal therapeutic strategies, including optimal timing of surgical resection in locally advanced tumors. Thus, acute and long-term side effects can be minimized while maintaining excellent survival. This goal can only be achieved through ongoing cooperative group studies. Advances in molecular understanding of these rare pediatric tumors may additionally help in the development of risk-adapted strategies. Site-specific details will be discussed.

39.1.11 Salvage Therapy

The treatment of recurrent germ cell tumors in children has not been studied systematically. Recurrent disease must be categorized based on histology (benign or malignant) and extent (local or distant). In addition, the first-line treatment has a substantial impact on both the choice of salvage treatment and prognosis. Thus, tumors that progress after surgery and watch-and-wait strategy commonly have a favorable prognosis with standard platin-based chemotherapy. In contrast, malignant tumors that relapse after first-line treatment are often resistant to further therapy, and prognosis is poor. Recurrent benign tumors (mature teratomas and most immature teratomas) must be treated with surgery. Chemotherapy has not yielded significant improvement in these benign tumors. One example that demonstrates this phenomenon is the "growing teratoma syndrome." A mixed tumor with teratoma and yolk sac tumor continues to grow despite normalization of markers. At surgery, only viable mature teratoma persists (Afifi et al. 1997). Of note, these growing teratomas retain the cytogenetic aberrations also present in malignant germ cell tumors (van Echten et al. 1997a, b). It may be concluded that in these tumors, terminal differentiation presents a way to evade cytotoxic treatment and to induce resistance to chemotherapy (Mayer et al. 2003a). For these tumors, alternative strategies with either immunomodulation (interferon) (van der Gaast et al. 1991) or antiangiogenetic therapy (Calaminus et al. 2009) have been applied with some success. Nevertheless, surgical resection is always required, even if intermittent stable disease can be achieved with such strategies. In 3–6% of adult cases, somatic transformation is evident.

The prospective assessment of salvage therapies in recurrent or refractory malignant pediatric germ cell tumors is limited by the small numbers of patients.

The treatment of recurrent malignant pediatric germ cell tumors is anecdotal. In contrast to adult patients, many children have local relapses and treatment may include intensive chemotherapy and local therapy (Schneider et al. 2001d). For these purposes a strategy that utilizes up-front chemotherapy followed by

Table 39.1.6 Pediatric treatment strategies

Drug	Doses	No. of cycles
US Children's Oncology Group: PEB (9048/8891;9049/8890)		
Cisplatin	20 mg/m^2, day 1, 2, 3, 4, 5 or 33 mg/m^2, day 1, 2, 3	3–4 cycles
Etoposide	100 mg/m^2, day 1, 2, 3, 4, 5 or 167 mg/m^2, day 1, 2, 3	
Bleomycin	15 U/m^2, day 1	
German MAKEI study group: PE and PEI (MAKEI 96)/SIOP CNS GCT I-II		
Cisplatin	20 mg/m^2, day 1,2,3,4,5	2–4 cycles
Etoposide	100 mg/m^2, day 1,2,3	
Ifosfamide	1500 mg/m^2, day 1,2,3,4,5	
French TGC study group: PVB and VIP (TGM 2011)		
Cisplatin	20 mg/m^2, day 1,2,3,4,5	Up to 3 cycles
Vinblastin	3 mg/m^2, day 1,2	
Bleomycin	15 U/m^2, day 1	
Cisplatin	20 mg/m^2, day 1,2,3,4,5	Up to 4 cycles
Etoposide	75 mg/m^2, day 1,2,3,4,5	
Ifosfamide	3,000 mg/m^2, day 1,2	
Italian GCT study group (PEB)		
Cisplatin	25 mg/m^2, day 1,2,3,4	Up to 4 cycles
Etoposide	100 mg/m^2, day 1,2,3,4	
Bleomycin	15 mg/m^2, day 2	
Brazilian TCG [PE (high-dose PE), IVB] (Lopes, 2009)		
Cisplatin	20 mg/m^2, day 1,2,3,4,5	5 cycles
Etoposide	100 mg/m^2, day 1,2,3,4,5	
HD-Cisplatin	30 mg/m^2, day 1,2,3,4,5	5 cycles
HD-Etoposide	120 mg/m^2, day 1,2,3,4,5	
Ifosfamide	1,500 mg/m^2, day 1,2,3	3 cycles
Velban	3 mg/m^2, day 1	
Bleomycin	15 mg/m^2, day 1	
SIOP central nervous system germ cell tumor protocol (SIOP CNS GCT) (HD-PEI) (Schmoll 2003)		
Cisplatin	100 mg/m^2, day 1,2,3,4,5	3 cycles (after one initial cycle of conventional PEI)
Etoposide	300 mg/m^2, day 1,2,3,4,5	
Ifosfamide	2,000 mg/m^2, day 1,2,3,4,5	
Plus autologous stem cell support plus G-CSF at day 7		
SIOP central nervous system germ cell tumor protocol (SIOP CNS GCT) (Carbo-PEI)		
Carboplatin	600 mg/m^2, day 1	2 cycles
Etoposide	100 mg/m^2, day 1,2,3,22,23,24	
Ifosfamide	1800 mg/m^2, day 22,23,24,25,26	
UK CCLG (Mann 2000)		
Carboplatin	600 mg/m^2, day 2	Until remission + 2 cycles
Etoposide	120 mg/m^2, day 1,2,3	
Bleomycin	15 mg/m^2, day 3	

During cisplatin therapy, intensive infusion therapy with 3 l/m^2/day accompanied by mannitol forced diuresis is mandatory. During ifosfamide, uroprotection with mesna is recommended

delayed tumor resection has proven effective. In selected patients, locoregional control can be supported by the combination of cisplatin chemotherapy and regional deep hyperthermia (Wessalowski et al. 1997a, 2003a). In addition, it is certainly helpful to concentrate surgical therapy of patients with recurrent malignant germ cell tumors in specific national surgical centers. This provides the opportunity to centralize

experience in these often delicate surgical procedures and to advance scientific research on salvage surgery.

Radiation therapy with at least 45 Gy for nonseminomatous germ cell tumors (Table 39.1.5) may also be considered to improve local control, in particular, in tumors not assessable to complete resection (Schneider et al. 2001d).

A multimodal strategy that combines chemotherapy, surgery, and possibly radiotherapy is necessary for recurrent malignant tumors. Trials in adult patients with recurrent or persistent malignant germ cell tumors have provided potential strategies for salvage chemotherapy. Complete responses from 50% to 77% have been obtained in patients, who relapsed after cisplatin therapy (Motzer et al. 2000). Combinations of paclitaxel, ifosfamide, and cisplatin; vinblastine, ifosfamide, and cisplatin; or vincristine, bleomycin, and cisplatin have been used. Autologous marrow transplantation has also been used to treat these adult patients (Einhorn et al. 2007). However, in particular, for extragonadal germ cell tumors, the therapeutic impact of high-dose chemotherapy is limited, if no local control can be achieved (Schneider et al. 2001d).

Retroperitoneal lymph node dissection (RPLND) has not been part of standard pediatric germ cell tumor treatment. Post-chemotherapy followed by RPLND may be an integral part of treatment in adolescent and adult males. These tumors may progress in the retroperitoneal lymph nodes, and residual teratoma may dedifferentiate into malignant germ cell tumor or somatic malignant differentiation (Carver et al. 2007a, b, c). Site-specific salvage therapies will be discussed with anatomic sites.

39.1.12 Late Effects

In the study of late effects of therapy, attention must be paid to those late effects from tumor and local therapy and those effects secondary to systemic therapy (Table 39.1.7).

Among the various possible late effects of germ cell tumors, local sequelae after surgery and/or radiotherapy must be distinguished from systemic late effects as a consequence of chemotherapy. Local effects can be caused both by tumor and by local treatment. For instance teratomas of the head and neck can involve the thyroid gland, which must then be removed with the tumor. As a consequence a proportion of children with cervical teratoma may suffer from insufficiency of the thyroid or parathyroid glands (Bernbeck et al. 2009a). Chronic endocrine insufficiency is also characteristic of hypophyseal germ cell tumors. In these tumors, diabetes insipidus may be the key symptom of the tumor. Diabetes insipidus will usually persist even after successful treatment of the germ cell tumors. Hypophyseal insufficiency may also result in other hormone deficiencies such as growth hormone deficiency.

Table 39.1.7 Potential late treatment effects

I. Late effects from tumor and local therapy
– CNS
Diabetes insipidus, GH, and other endocrine deficiencies
Hemianopsia, cranial nerve palsies, bone growth
– Head and neck tumors – hypothyroid, tracheal malacia
– SCT – incontinence
– Gonadal – sterility, lack of function
– Polyembryoma
– Mixed malignant germ cell tumor
Teratoma or immature teratoma with malignant GCT elements
Teratoma with other malignant element (e.g., squamous cell carcinoma)
II. Late effects from systemic therapy
– Cisplatin – ototoxicity and renal toxicity, secondary malignancy
– Bleomycin – pulmonary dysfunction and cutaneous toxicity
– Etoposide – secondary leukemia
– Ifosfamide – renal toxicity

Sacrococcygeal teratomas are often very large at presentation. They may distort the anatomic situation of the pelvic floor so that the muscles of the pelvic floor have to be reconstructed during tumor resection. However, still some patients may develop palsy of the pelvic floor, in particular, if a malignant tumor infiltrates the nerves of the sacral plexus. As a result, these patients may be incontinent for stool and/or urine, or they may suffer from chronic obstipation. The risk of recurrent urinary infections is also increased. Since many germ cell tumors grow to a considerable size, a broad surgical approach is required, thus giving rise to scars at considerable size. Nevertheless, as presented in the respective chapters, most patients even with gross tumors grow up with a good quality of life and without mutilation. To achieve this goal, the possibility to apply up-front chemotherapy prior to surgery should be considered in all malignant germ cell tumors.

The issue of chemotherapy-related late effects is multifactorial and varies with the different chemotherapy combinations applied according to the different protocols.

Cisplatin era has greatly improved survival in children with malignant germ cell tumors. However, significant toxicity and late effects have occurred. Hearing impairment, in particular, high tone loss, was noted in a substantial proportion of pediatric patients treated with high-dose cisplatin (Cushing et al. 2004a). However, individual audiograms have already documented significant hearing loss with both standard- and high-dose cisplatin (Li et al. 2004). Amifostine, as a protectant, did not lessen ototoxicity (Marina et al. 2003). Young children are particularly sensitive to toxic effects of cisplatin. Importantly, ototoxicity in a young child may significantly impair speech, academic, and social development (Knight et al. 2005).

A study in adults suggests that cisplatin ototoxicity may be associated with specific glutathione S-transferase genotypes (Oldenburg et al. 2007). In addition, genetic polymorphism of the megalin gene (Riedemann et al. 2008) may eventually provide a diagnostic tool to assessing the risk of ototoxicity prospectively. These markers have not yet been studied in children.

Nephrotoxicity may be enhanced when cisplatin and ifosfamide are used concurrently.In particular, children may develop tubulopathy with loss of electrolytes and glucose (secondary Fanconi syndrome). Therefore, renal function and urinary excretion of electrolytes should be monitored during follow-up in order to prevent renal osteopathy.

The risk of pulmonary toxicity of bleomycin in toddlers and infants is controversial. In adult germ cell tumors, there are reports on an increased risk of cardiovascular disease, including atherosclerosis and coronary disease. However, there are no comparable long-term follow-up data available for patients treated for a germ cell tumor during childhood. However, in the German MAKEI registry, two patients are documented, who developed lethal pulmonary fibrosis and pulmonary failure after bleomycin and anesthesia required for tumor resection (Göbel et al. 2000a). In adults, the risk of lethal pulmonary toxicity is estimated to be approximately 1% (Osanto et al. 1992). Most adult patients develop some gradual impairment of pulmonary function during bleomycin chemotherapy. However, these changes are mostly intermittent and resolve after cessation of chemotherapy. Nevertheless, since an increased pulmonary sensitivity is suspected for children and since pulmonary function cannot be monitored in infants, most pediatric protocols have either reduced bleomycin doses, reduced chemotherapy to a two-agent regimen, or replaced bleomycin with ifosfamide.

The risk of secondary neoplasms such as therapy-related acute myelogenous leukemias has been debated intensively, both for adult and pediatric patients treated with etoposide. According to the MAKEI series, the 10-year cumulative risk of secondary leukemia can be estimated to be approximately 1% in patients treated with chemotherapy alone and 4.2% in patients treated with both radio- and chemotherapy (Schneider et al. 1999). In the US pediatric intergroup study, there were four cases of acute myelocytic leukemia. None were associated with 11q23 abnormality, supporting that the regimen commonly prescribed for childhood germ cell tumors only have a low leukemogenic potential.

In this context, it should also be noted that some malignant germ cell tumors, in particular, malignant mediastinal nonseminomatous germ cell tumors, may be associated with concurrent or metachronous leukemia. However, this leukemic clone is intrinsic to the germ cell tumor and presents a somatic malignant transformation within the germ cell tumor. This is proven by the observation that the isochromosome 12p, which is pathognomic of the germ cell tumor, is also detectable in the leukemic cell (Orazi et al. 1993).

In adult patients, chemotherapy for malignant germ cell tumors is associated with a significant long-time risk of cardiovascular disease. Thus, the risk of myocardial infarction, angina pectoris, and heart failure is increased compared to healthy adults of the same age group (Gietema et al. 1992; Bokemeyer et al. 1996; van den Belt-Dusebout et al. 2006). Compared to adults, no comprehensive data on long-term cardiovascular risk for children treated with chemotherapy is currently available. However, considerable research activities are currently focusing on the issue of cancer survivorship. This data may then assist in evaluating different therapeutic strategies for childhood germ cell tumors that take both the therapeutic efficacy and long-term sequelae of therapy into account. The quality of semen is very poor in adults, even in those patients not treated with chemotherapy. This has not been well investigated in adults who were treated for germ cell tumors as children.

39.2 Extragonadal Germ Cell Tumors

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Germ cell tumors include a group of tumors that is highly heterogeneous regarding their clinical and histologic appearance. During childhood and adolescence, approximately half of all germ cell tumors develop at extragonadal midline sites. Sacrococcygeal germ cell tumors constitute the most frequent tumor in neonates, and extracranial germ cell tumors account for 14% of all cancers in adolescents of the 15–19 age group. Accordingly, an epidemiological analysis of patients reported to the German GCT trials from 1981 to 2000 showed a bimodal age distribution with a small peak during infancy and a larger peak after puberty (Schneider et al. 2004b). These separate groups were marked by distinct clinical and molecular features. The distribution of extragonadal tumor sites by age is shown in Figs. 39.1.1 and 39.1.2 of Sect. 39.1.1.

Experience gained in the successful chemotherapy of testicular germ cell tumors in adults has successfully been translated to the treatment of childhood extragonadal germ cell tumors. Several prospective trials of different national study groups have demonstrated that cis- or carboplatin-based combination chemotherapy is effective in extragonadal germ cell tumors, too (Kapoor et al. 1995, Cushing et al. 2004b; Göbel et al. 2000b; Lopes et al. 2009a; Mann et al. 2000b). In addition, substantial reduction of cumulative chemotherapy has become possible with the optimization of multimodal therapeutic strategies, including optimal timing of surgical resection in locally advanced tumors. Thus, acute and long-term side effects can be minimized, while maintaining excellent survival. This goal can only be achieved through ongoing cooperative group studies. Advances in molecular understanding of these rare pediatric tumors may additionally help in the development of risk-adapted strategies (Oosterhuis and Looijenga 2005b).

39.2.1 Histogenesis, Biology, and Histology of Extragonadal Germ Cell Tumors

These aspects are extensively discussed in Sect. 39.1. In summary, the histologic appearance of extragonadal germ cell tumors is undistinguishable from that of their gonadal counterparts. Moreover, within the corresponding age groups, they share the same genetic aberrations such as the isochromosome 12p or deletion of 1p and 6q. At the epigenetic level, both gonadal and extragonadal germ cell tumors show erasure of genomic imprinting, substantiating the holistic concept of Teilum that all germ cell tumors arise from primordial germ cells (Teilum et al. 1975b).

Nevertheless, some peculiar and site-specific features have to be considered. Thus, the histologic differentiation may be restricted to specific subtypes such as teratoma and yolk sac tumor in the coccygeal region (Göbel et al. 2001; Harms and Jänig 1986) and yolk sac tumor in the vagina (Mauz-Körholz et al. 2000). At these sites, no germinomatous tumors can be observed.

In addition, the development of germ cell tumors may be restricted to specific age groups. Sacrococcygeal or vaginal germ cell tumors only develop in prepubertal children, while ovarian and central nervous system germ cell tumors mainly develop during and after puberty (Schneider et al. 2004b). Last, some extragonadal germ cell tumors may be associated with specific genetic aberrations such as Klinefelter's syndrome in mediastinal germ cell tumors, while this constellation is not observed at other sites (Nichols et al. 1987b; Schneider et al. 2002b). These clinical observations illustrate that some yet unknown site-specific environmental factors significantly modulate the development as well as histologic and clinical appearance of extragonadal germ cell tumors. In how far such factors also impact on therapy is currently speculative.

39.2.2 Pathology

Germ cell tumors show numerous histologic subtypes; however, the microscopic morphology of a distinct histologic subentity is undistinguishable regardless of age at diagnosis, tumor site, and genetic background (Dehner 1983b). Thus, tissue from ovarian cystic teratoma, a tumor arising from premeiotic cells, is undistinguishable from mature cystic teratoma of the sacrococcygeal region or the central nervous system. Currently, germ cell tumors are most commonly classified according to the World Health Organization revised classification for testicular, ovarian, and central nervous system tumors (Young 2005a; Kleihues et al. 1993; Mostofi and Sobin 1993; Serov and Scully 1973). Still, there are some

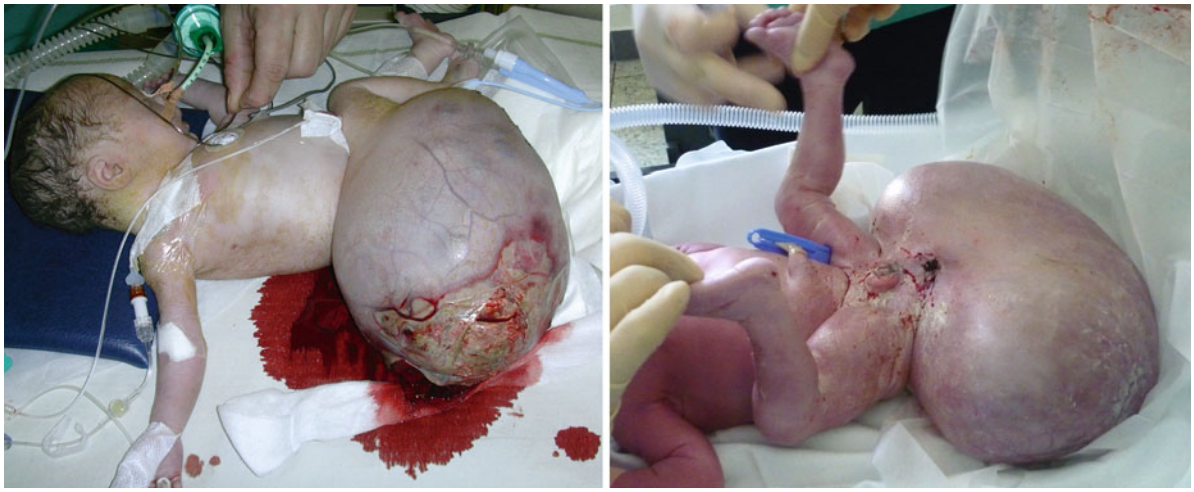

Fig. 39.2.1 Clinical presentation of neonatal sacrococcygeal teratomas. The tumor shown to the left is incompletely covered with skin and ruptured during delivery (cesarean section), leading to hemorrhagic shock

inconsistencies in the site-specific classification, in that different terms are used for histologically and biologically identical tumors, i.e., seminomas of the testis, dysgerminomas of the ovary, and germinoma of the CNS. These inconsistencies are mainly explained by the historical development of the site-specific classifications. However, in all classification systems, the approach to mixed malignant germ cell tumors composed of different histologic components is comparable. Thus, all different histologic entities present in each single tumor are listed separately so that a specific description is provided that may assist in the optimal planning of the multimodal therapy. For instance, in a mixed malignant germ cell tumor with germinoma and teratoma, a 2-cm tumor residue after chemotherapy should be interpreted different from a 2-cm residue of a pure germinoma; the first could represent residual teratoma, whereas a residue of pure germinoma may be pure scar tissue.

The histologic classification of these tumors is shown in Table 39.1.3 of Sect. 39.1.1. The pathologic features of each histologic subtype are discussed separately in Sect. 39.1.1 too.

39.2.3 Clinical Diagnosis

39.2.3.1 Clinical Symptoms

The diagnosis of extragonadal germ cell tumors primarily depends on the clinical and radiographic assessment as well as the evaluation of the "specific" tumor markers AFP and β-HCG. In most patients, germ cell tumors present as considerably large indolent tumors. In contrast, childhood testicular germ cell tumors are mainly diagnosed at a comparably small size, since in young infants these tumors are detected by the parents while the diapers are changed. In analogy, vaginal yolk sac tumors are mostly diagnosed at comparable moderate size, because these may become apparent after vaginal bleeding.

Regardless of benign or malignant histology, large tumors may result in significant local complications. Thus, head and neck teratomas may result in acute life-threatening airway obstruction, requiring an anticipating and qualified perinatal management [Fig. 19.1 in Chap. 19. (Head and Neck Teratomas)]. Sacrococcygeal teratomas may cause tumor bleeding if extrapelvic cysts rupture during vaginal delivery (Fig. 39.2.1). On the other hand, sacrococcygeal germ cell tumors may lead to chronic obstipation if they show predominantly intrapelvic extension (Fig. 39.2.2). Some sacrococcygeal yolk sac tumors may lead to skeletal metastases including the vertebral columns (Fig. 39.2.3). Spinal invasion may then lead to acute paralysis. Vaginal yolk sac tumors may lead to vaginal bleeding.

At other sites, the diagnosis even of small tumors is also guided by local symptoms and complications. Thus, CNS germ cell tumors of the hypophyseal region frequently present with diabetes insipidus, or pineal tumors may result in symptoms resulting from increased intracranial pressure or in vertical ocular

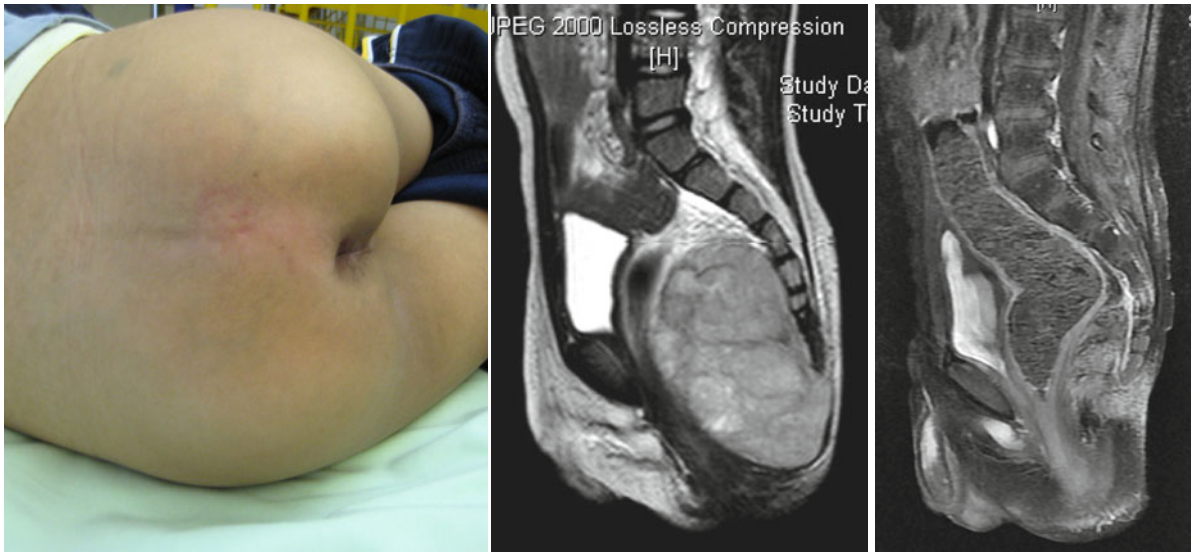

Fig. 39.2.2 Sacrococcygeal yolk sac tumor (Altman III/IV) in a 3-year-old boy: clinical presentation and MRI prior to (*left*) and after (*right*) chemotherapy with three cycles of cisplatin, etoposide, and etoposide

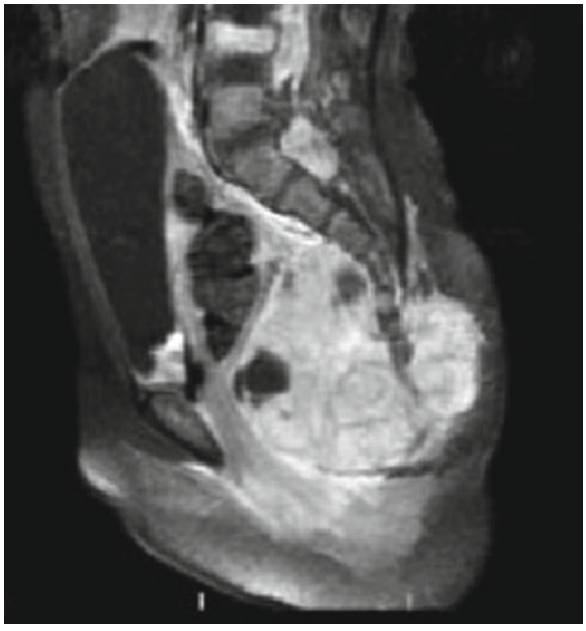

Fig. 39.2.3 Sacrococcygeal yolk sac tumor (Altman III) of a 2-year-old girl with bone metastasis in lumbar spine

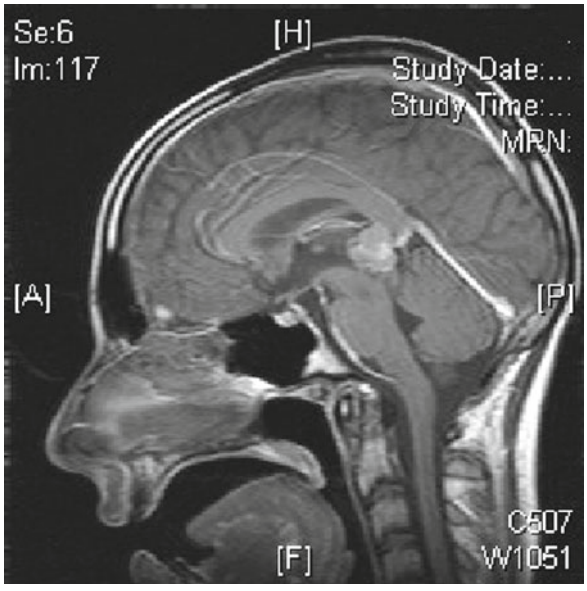

Fig. 39.2.4 Pineal mixed malignant germ cell tumor in a 15-year-old male

paralysis (Parinaud's syndrome) (Fig. 39.2.4) (Cho et al. 1998; Diez et al. 1999; Hieda and Fukui 2008). Apart from this, unspecific personality changes have also been reported. Rarely, differentiated elements within teratomas may result in endocrinological pertubances, e.g., by inadequate hormone secretion (Esik et al. 1994; Lam and Cheung 1996; Yassa et al. 2008). Last, due to their specific location at very sensible midline sites, CNS germ cell tumors often lead to obstructive hydrocephalus, as it is demonstrated in Fig. 39.2.5, showing an infant with a huge teratoma.

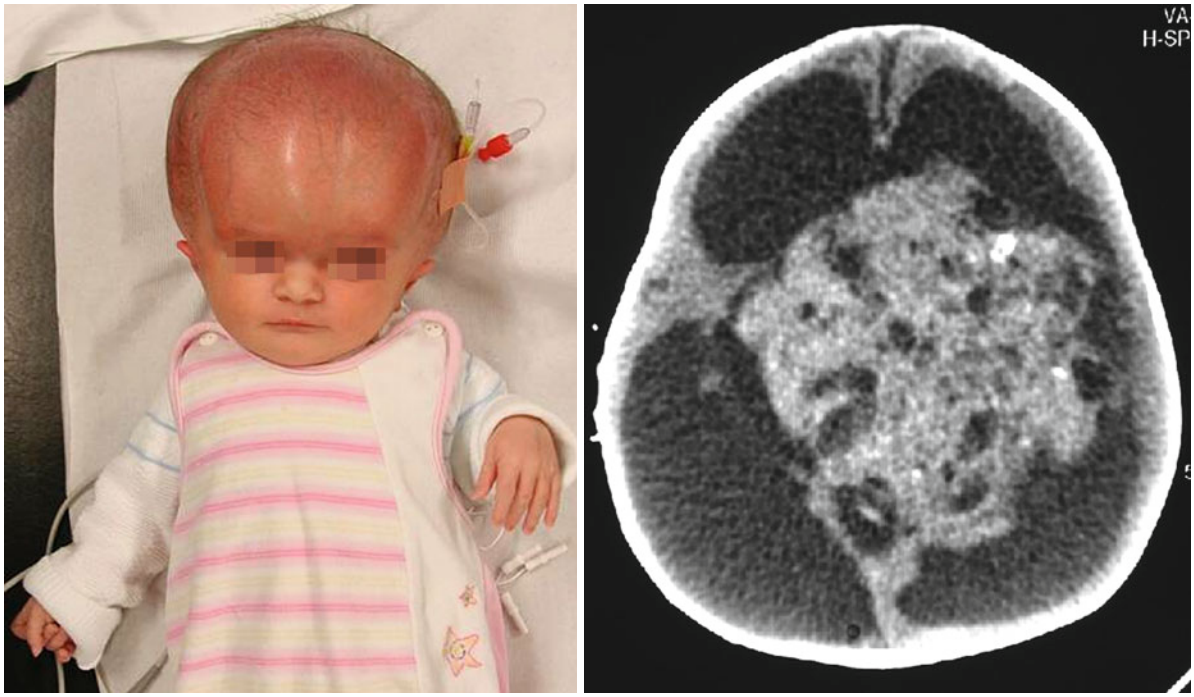

Fig. 39.2.5 One-month-old infant with an unresectable intracranial teratoma

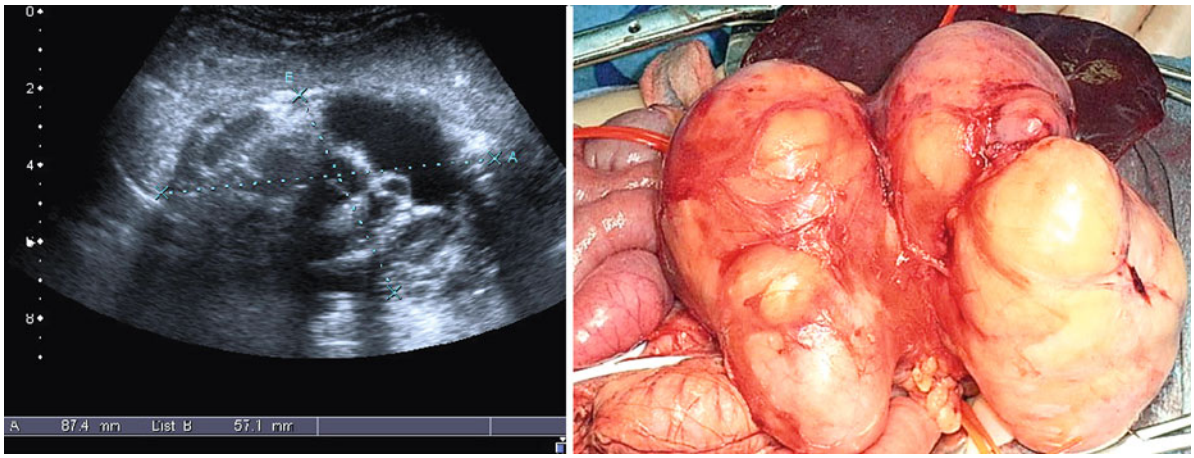

Fig. 39.2.6 Retroperitoneal teratoma in a 1-year-old girl: ultrasound and operative situs

39.2.4 Diagnostic Assessment

The diagnostic assessment is also outlined for sacrococcygeal, retroperitoneal, and central nervous system germ cell tumors in Tables 39.2.1–39.2.3. The medical history and physical examinations should consider signs of congenital malformations such as anal atresia (Currarino et al. 1981) or sex-chromosomal aberrations such as Ullrich-Turner and Klinefelter's syndrome, which may be associated with specific subtypes of germ cell tumors. In each child, the pubertal status has to be documented. Both testes have to be palpated. Rarely, a retroperitoneal teratoma may interfere with testicular descensus, so that a "retroperitoneal" tumor may arise in an undescended testis (Schwabe et al. 2000).

In sacrococcygeal tumors (Table 39.2.1), a rectal examination should be performed to palpate for

Table 39.2.1 Specific diagnostic strategy in sacrococcygeal germ cell tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Obstipation? Continence? Urinary retention? Anal atresia/malformation?
Phys. examination	Rectal examination: intrapelvic tumor component/relation to rectum. Anal sphincter tone?
Audiometry	Sensorineural hearing loss?
Laboratory assessment	
– Creatinine clearance/cystatin c	Assessment of renal function
– AFP	Malignant GCT with yolk sac tumor (consider age-related reference values)
– LDH	Unspecific marker with prognostic impact
Radiographic assessment	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to rectum, extension into spinal canal, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to rectum, extension into spinal canal, lymph node metastases, vertebral metastases
Chest X-ray	Lung metastases
Chest CT	Lung (micro-) metastases
Brain MRI	CNS metastases (indicated in case of pulmonary or visceral metastases and/or neurological symptoms)
Bone scan	Skeletal metastases (indicated in case of pulmonary or visceral metastases and/or bone pain)
Histologic assessment	
H&E	Classification according to WHO, in teratoma grading of immaturity according to Gonzalez-Crussi or Skullbeck
AFP	Yolk sac tumor (microfoci in teratoma)

Table 39.2.2 Specific diagnostic strategy in retroperitoneal germ cell tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Obstipation? Klinefelter's syndrome? Maldescensus testis? Ullrich-Turner syndrome? Gynecological anamnesis?
Phys. examination	Tumor size, pubertal status, testicular palpation
Audiometry	Sensorineural hearing loss?
Laboratory assessment	
– Creatinine clearance/cystatin c	Assessment of renal function
– AFP	Malignant GCT with yolk sac tumor (consider age-related reference values)
– β-HCG	Malignant GCT with choriocarcinoma
– LDH	Unspecific marker with prognostic impact
Radiographic assessment	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to the intestine, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to the intestine, lymph node metastases
Chest X-ray	Lung metastases
Chest CT	Lung (micro-) metastases
Brain MRI	CNS metastases (indicated in case of choriocarcinoma and/or pulmonary or visceral metastases and/or neurological symptoms)
Bone scan	Skeletal metastases (indicated in case of pulmonary or visceral metastases and/or bone pain)
Histologic assessment	
H&E	Classification according to WHO, in teratoma grading of immaturity according to Gonzalez-Crussi or Skullbeck
AFP	Yolk sac tumor (microfoci in teratoma)
β-HCG	Choriocarcinoma
HPLAP, OCT3/4	Seminoma
CD30	Embryonal carcinoma

Table 39.2.3 Specific diagnostic strategy in central nervous system germ cell tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Signs of intracranial hypertension? Signs of diabetes insipidus. Pubertal development
Phys. examination	Complete neurological assessment: cerebral palsy? Parinaud's phenomenon? Klinefelter's syndrome? Pubertal status? Testicular palpation
Ophthalmology including perimetry	Intracranial hypertension? Hemianopsia?
Audiometry	Sensorineural hearing loss?
Phys. examination	Complete neurological assessment: cerebral palsy? Parinaud's phenomenon? Klinefelter's syndrome? Pubertal status? Testicular palpation
Laboratory assessment	
– Serum and urine osmolarity	Diabetes insipidus
– Serum sodium	Diabetes insipidus
– Creatinine clearance	Assessment of renal function
– AFP (serum + CSF)	Malignant GCT with yolk sac tumor (cutoff 25 µg/L)
– β-HCG (serum + CSF)	Malignant GCT with choriocarcinoma (cutoff 50 U/µl)
– HPLAP	Malignant GCT with germinoma
– LDH	Unspecific marker with prognostic impact
– CSF cytology	Detection of (micro-) metastatic spread
Radiographic assessment	
Brain MRI	Tumor extension, uni- or bifocal disease, ventricular or brain metastases
Spinal MRI	Spinal metastases
Chest X-ray	Lung metastases
Abdominal ultrasound	Liver metastases, exclusion of renal disease
Bone scan	Skeletal metastases (indicated in case of pulmonary or visceral metastases and/or bone pain)
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)

intrapelvic tumor extension and to consider a potential proximity to or infiltration of the rectum. The anal sphincter tone should also be documented preoperatively, since in some rare patients, paralysis of the pelvic floor may develop following surgery. These examinations should also be performed during follow-up investigations.

The first radiographic assessment is usually made by ultrasound, which should always include the draining lymph nodes. Sonography is the most commonly applied initial imaging technique and is usually followed by magnetic resonance imaging, which should always depict the tumor in all three dimensions. For sacrococcygeal tumors, the intrapelvic anatomy, i.e., the association to the rectum, has to be carefully considered, since this may have important implications for surgical therapy. In addition, any extension into the spinal canal should be excluded with MRI (Jelin et al. 2009; Ribeiro et al. 1999). Rarely intrapelvic teratomas may develop as a manifestation of the Currarino triad, which describes the association of anal atresia, sacral hemiagenesis, and intrapelvic masses such as dermoid cyst or teratoma (Currarino et al. 1981).

Due to their crucial importance for the categorization of childhood germ cell tumors, the serological markers alpha$_1$-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are discussed in detail in Sect. 39.1.1. Because of the wide variation in levels at birth, especially with infants of less than 40 weeks' gestational age, and the wide variability in $t_{1/2}$ at different ages within the first year of life, difficulties arise in interpreting decay of serum AFP as an indication of residual or recurrent GCT in infants younger than 12 months (Schneider et al. 2001f; Blohm et al. 1998b).

Increasing levels of serum AFP, however, are not necessarily indicative of tumor progression. Abrupt escalation in serum AFP can occur after chemotherapy-induced tumor lysis (Schneider et al. 2001f). Otherwise, the decline of AFP during chemotherapy of yolk sac tumor strongly indicates a favorable response to therapy and thus favorable prognosis (Calaminus et al. 1991). Spurious persistence of

elevated serum AFP may reflect an alteration in hepatic function from such conditions as viral hepatitis (hepatitis B, hepatitis C, and human immunodeficiency virus–associated hepatitis), cholestasis secondary to anesthesia, metabolic disease (e.g., tyrosinemia type I), or exposure to phenytoin or methotrexate. Other neoplastic conditions associated with elevated serum AFP include hepatoblastoma, hepatocellular carcinoma, pancreaticoblastoma, pancreatic, gastrointestinal, and bronchial adenocarcinomas (Schneider et al. 2001f).

AFP is not only helpful in detecting significant yolk sac tumor components but may also assist in prognostic assessment. In a large cooperative analysis of adult germ cell tumors, high AFP and/or β-HCG levels indicated poor prognosis (International-Germ-Cell-Cancer-Collaborative-Group 1997). In the British childhood cancer studies, high AFP levels above 1,000 μg/L were associated with unfavorable outcome (Mann et al. 1989b, 2000b). Furthermore, an inadequate decline of AFP that does not follow its half time of 5–7 days indicates pure response to chemo or tumor progression after tumor resection (Calaminus et al. 1991).

The most frequent for significant rise of β-HCG is pregnancy. Therefore, in case of suspected GCT and elevated β-HCG, pregnancy must be excluded with other techniques, e.g., ultrasound. Elevation of serum β-HCG in patients with germ cell tumors implies the presence of clones of syncytiotrophoblasts, such as choriocarcinoma, or of syncytiotrophoblastic giant cells, found frequently in germinomas (pure seminomas or dysgerminomas) and occasionally in adult embryonal carcinoma. Immunoperoxidase staining of tumor for β-HCG detects these hormone-containing elements.

39.2.5 Staging of Extracranial Extragonadal Germ Cell Tumors

Pure teratomas of childhood do not metastasize. However, since they may include microscopic foci of malignant yolk sac tumor, the draining lymph nodes should be examined with ultrasound or MRI, and an initial chest X-ray can be performed in order to document absence of metastases. It should be noted that teratomatous tumors arising after puberty may sometimes be associated with metastatic spread. Thus, clinical staging with ultrasound, MRI, and chest X-ray is certainly justified. If absence of metastases is documented, the follow-up of childhood teratomas should primarily focus on the primary tumor site, since relapses most commonly develop locally.

Malignant yolk sac tumors of childhood show a tendency to metastasize into the locoregional lymph nodes and into the lungs, justifying a limited staging assessment focusing on these sites. Currently, there is no prospectively proven evidence as to whether pulmonary micrometastases detected with CT scans of the lungs are therapeutically and prognostically relevant. In fact, pulmonary metastases commonly of childhood yolk sac tumor commonly show a favorable response to platin-based chemotherapy and extremely rarely require surgical treatment. However, germ cell tumors with pulmonary micrometastases are certainly eligible to intensive chemotherapy with four cycles of chemotherapy so that CT scans are commonly used and currently recommended in order to increase the accuracy of clinical staging.

Rarely, metastases at other sites such as the liver, the bones, or the CNS are noted. However, these metastases almost never present in the absence of lung metastases or site-specific symptoms such as bone pain (Calaminus et al. 2003). Therefore, clinical staging should be expanded to bone scan and MRI of the brain if lung metastases are diagnosed or if specific symptoms such as bone pain are reported.

39.2.6 Clinical Staging Systems for Extracranial Germ Cell Tumors

Different staging systems are used for extragonadal malignant germ cell tumors, which all have several advantages and disadvantages. The main problem is that extragonadal germ cell tumors may arise at different anatomical size, which of course cannot be considered in a general staging system. Therefore, the currently applied staging systems reflect general characteristics such as infiltration into neighboring organs and metastatic spread into the lymph nodes or the lungs or other visceral organs. The German MAKEI group is currently applying a modified TNM staging system for soft tissue sarcomas, according to which tumor size (<5 cm vs. >5 cm diameter) and local infiltration are considered for T-staging. Lymph node and distant metastases are counted separately as either negative or positive (Table 39.2.4). For therapy stratification, the completeness of resection is considered as a separate variable.

In contrast, the staging system according to the US COG also integrates information on resection status as well as the initial surgical procedure. Thus, all patients who undergo a biopsy prior to the start of chemotherapy are considered stage III (Table 39.2.5). A main advantage of this staging system is that it is similarly applied to gonadal germ cell tumors, facilitating comparison of prognostic and therapeutic data regardless of site. However in contrast to the TNM system, biopsy procedures will always upstage tumors to stage III, irrespective of anatomical stage.

39.2.7 Germ Cell Tumors of the Central Nervous System

Since CNS germ cell tumors are described extensively in this series' book on CNS tumors, only a brief description of the general diagnostic and therapeutic strategies is provided in this chapter.

Primary intracranial germ cell tumors primarily develop during adolescence and young adulthood. They may be located in the pineal gland (62%) or suprasellar region (31%), or they may span both areas (7%) (Balmaceda and Finlay 2004; Bamberg et al. 1999; Calaminus et al. 2005). Symptomatology depends on site, growth pattern, and histology of the tumor and may include personality changes, visual disturbances, diabetes insipidus, hypopituitarism, Parinaud's syndrome (convergence nystagmus), anorexia, and precocious puberty. Histologically, two thirds of the tumors are germinomas, and the rest are nongerminomatous, some mixed with yolk sac tumor, choriocarcinoma, or teratocarcinoma.

The clinical assessment of central nervous system germ cell tumors is outlined in Table 39.2.3. Since hypophyseal germ cell tumors may induce diabetes insipidus, specific attention should be paid to the serum electrolytes as well as serum and urine osmolarity. The presence of diabetes insipidus would have significant impact on infusion therapy during chemotherapy, since severe electrolyte imbalances may develop during intensive infusion therapy required during platin chemotherapy (Bryant et al. 1994).

It is important to note that CNS germ cell tumors show a marked tendency to metastasize through the cerebrospinal fluid. Thus, metastases within the ventricular system as well as drop metastases to the spine may occur (Alapetite et al. 2002, 2010; Calaminus et al. 2002). Extracranial spread to lung and bones has also been reported, however very rarely. Considering their tendency to spread within the cerebrospinal fluid, cytological evaluation after lumbar tap or of cerebrospinal fluid collected during surgery is absolutely mandatory for initial staging. If cytological examination is not performed perioperatively, tumors should be considered potentially metastatic, with a significant impact on local treatment, i.e., radiotherapy (Calaminus et al. 1997a).

Table 39.2.4 Staging system for extragonadal germ cell tumors adapted from the TNM staging system for soft tissue sarcomas

Category		Parameters	
Local stage			
T	1a	No infiltration of neighboring organs	<5 cm
	1b		>5 cm
	2a	Infiltration of neighboring organs	<5 cm
	2b		>5 cm
N	0	No lymphatic metastases	
	1	Lymphatic metastases	
M	0	No distant metastases	
	1	Distant metastases	

Table 39.2.5 US COG staging system for gonadal and extragonadal germ cell tumors

Children's Oncology Group staging of extragonadal germ cell tumors	
I	Complete resection at any site, coccygectomy for sacrococcygeal site, negative tumor margins. No evidence of metastases. Appropriate marker decline
II	Microscopic residual; lymph nodes negative
III	Gross residual disease or biopsy ony; Lymph node involvement with metastatic disease; retroperitoneal nodes positive or negative
IV	Metastatic disease including liver

There is no specific staging system for central nervous system germ cell tumors. Thus, they are staged in analogy to other CNS tumors such as medulloblastoma (Chang et al. 1969). Mainly, the presence of tumor cells in the cerebrospinal fluid as well as metastases to different sites of the CNS is considered. Local radiotherapy is planned according to this initial staging, with inclusion of craniospinal irradiation in micrometastases and an additional boost to any visible metastases apparent on MRI.

AFP and β-HCG should be measured both in the serum and the cerebrospinal fluid, because they indicate secreting malignant nonseminomatous germ cell tumors. Of note, discrepant levels between serum and cerebrospinal fluid may be detected in some patients. There is considerable debate regarding the appropriate cutoff levels for AFP and β-HCG, since in some rare patients histologically pure germinoma may be associated with significant β-HCG secretion. However, in the current international SIOP study on CNS germ cell tumors, cutoff levels of AFP, 25 μg/l, and β-HCG, 50 IU/μl, have been defined (Calaminus et al. 1994, 2005, 2002). Tumors associated with higher levels either in the serum or the cerebrospinal fluid are considered secreting tumors and selected for more intensive chemotherapy with cisplatin instead of carboplatin and higher irradiation doses. Of note, these tumor markers also assist in establishing a clinical diagnosis in that a significant elevation is considered sufficient for the clinical diagnosis of a malignant germ cell tumor even without biopsy. Last, high AFP levels above 1,000 μg/L may be used for therapy stratification in the current SIOP protocol.

39.2.8 Treatment Overview

For all extragonadal germ cell tumors, an individualized multimodal treatment plan has to be chosen that takes histology, the site of origin, and stage into account. The treatment of teratoma is surgical; apart from single-case reports (Garre et al. 1996), there is no evidence of significant therapeutic effects of chemotherapy in pure teratomas (Göbel et al. 1997, 1998a; Marina et al. 1999b). In malignant germ cell tumors, surgical resection is also of vital importance for successful treatment, since extragonadal germ cell tumors show a high tendency to relapse at the site of origin. Therefore, complete resection constitutes the mainstay of treatment (Göbel et al. 2001; Schneider et al. 2000b). In rare, circumscribed, and nonmetastatic malignant germ cell tumors, patients may not require additional chemotherapy following complete surgical resection. However, in most extragonadal germ cell tumors, chemotherapy is indicated to consolidate remission after initial resection. Alternatively, up-front chemotherapy may be applied to facilitate complete resection on delayed surgery. Radiotherapy is rarely applied in extragonadal germ cell tumors. In contrast, it is commonly applied in central nervous system germ cell tumors, in which it may partly replace surgical resection as a measure to achieve local tumor control (Bamberg et al. 1999; Calaminus et al. 2005).

Chemotherapy is given according to the regimens also administered for gonadal germ cell tumors (see Table 39.1.4 in Sect. 39.1.1).

39.2.9 Principles of Surgery of Extragonadal Extracranial Germ Cell Tumors

Surgical resection is the therapy of choice in benign tumors, such as teratomas. With malignant lesions, removal is indicated, if possible. However, given the availability of effective chemotherapy, resection should not be undertaken to the point of sacrificing vital structures. In this situation, biopsy may be appropriate. Biopsy will not only support, confirm, and specify clinical diagnosis but also opens perspectives for genetic analysis and molecular research.

It must be emphasized that surgical recommendations may differ significantly for children and adolescents. After initial chemotherapy, second-look surgery serves to assist in achieving complete response in selected patients. Specific surgical strategies for specific extragonadal germ cell tumors of the mediastinum and the head and neck region are described in Chap. 19 and below for sacrococcygeal germ cell tumors.

39.2.10 Principles of Chemotherapy for Extragonadal Germ Cell Tumors

Substantial improvements in the cure rates for pediatric germ cell tumors have occurred, stemming in large part from the evolution of effective chemotherapeutic

strategies, most developed for the larger adult population with these neoplasms. Most pediatric germ cell tumor trials are limited by the small numbers of tumors at each site of origin with specific histology and stage.

Most chemotherapeutic studies have been conducted in patients with testicular and extragonadal tumors, primarily with advanced or disseminated disease. These data indicated that extragonadal germ cell tumors show a similar response to cisplatin-based combination chemotherapy as gonadal germ cell tumors do (Mann et al. 2000b; Göbel et al. 2000). However, mediastinal germ cell tumors constitute the largest subgroup of extragonadal germ cell tumors in adults, and they commonly have an unfavorable prognosis (Ganjoo et al. 2000). Therefore, strategies for chemotherapy intensification have been proposed that incorporate dose-escalated chemotherapy as well as high-dose chemotherapy with autologous stem cell transplantation (Bokemeyer et al. 2003; Schmoll et al. 2003).

Pediatric studies have mirrored the adult experience. Combination chemotherapy has been found to be superior to single or dual agents, and the addition of cisplatin has increased the efficacy of these regimens (Billmire et al. 2003; Billmire et al. 2004a; Cushing et al. 2004b; Rogers et al. 2004b; Lopes et al. 2008, 2009a; Göbel et al. 2000). In the intergroup study conducted by the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG), PEB, as standard treatment, was compared to a combination of high-dose cisplatin plus etoposide and bleomycin (Cushing et al. 2004b). This regimen did differ from adult PEB treatments because bleomycin was not administered weekly. Patients with localized gonadal germ cell tumors were treated with standard PEB. All other gonadal and all extragonadal germ cell tumors were randomized to standard PEB or a regimen with high-dose cisplatin (200 mg/m^2). Although tumor control was better in high-risk patients who received high-dose cisplatin, significant toxicity appeared to limit its use.

Studies conducted by the United Kingdom Children's Cancer Study Group suggest the superiority of carboplatin over standard-dose cisplatin in reducing permanent toxicity. Comparison was not made, however, to high-dose cisplatin (Mann et al. 1998; Mann et al. 2000b).

The Brazilian pediatric germ cell tumor group applied a response-based strategy. Bleomycin was omitted for both intermediate- and high-risk patients (Lopes et al. 2008, 2009a). Cisplatin, at 30 mg/m^2/day for 5 days, was administered to high-risk patients. After three cycles patients from both risk categories, who did not achieve CR, were switched to ifosfamide, vinblastine, and bleomycin. Though the study was limited by small sample size, some patients were treated successfully without bleomycin. In addition, a rationale for response-based treatment was suggested (Lopes 2009). Marrow-ablative doses of carboplatin and etoposide followed by autologous marrow reinfusion may provide a method of salvaging patients who experience relapse or whose disease proves refractory to treatment.

The French group has utilized both carboplatin- and cisplatin-based regimen. In the late 1980s and 1990s, carboplatin-based regimen have been applied, with doses of carboplatin at 400 mg/m^2/cycle (Baranzelli et al. 1999b, 2000a), which is considerably lower than in the British studies. In this study, inferior response rates have been reported, in particular, for extragonadal germ cell tumors (Baranzelli et al. 1999b). However, patients could be salvaged with second-line cisplatin-based regimen. In the current studies, a combination of cisplatin, etoposide, and ifosfamide is applied, using a response-based strategy. Thus, patients receive two additional cycles after complete response, summing up to a median of three cycles in intermediate-risk patients and five cycles in high-risk patients.

In the German MAKEI protocols, therapy is stratified according to site, stage, and completeness of tumor resection (Göbel et al. 1999, 2000). In locally advanced and metastatic tumors, up-front chemotherapy after clinical diagnosis based on markers or biopsy is strongly advocated. In completely resected, low-stage tumors, a watch-and-wait strategy is chosen, or patients are treated with two to three cycles of a two-agent regimen including cisplatin and etoposide. In all other tumors, cisplatin and etoposide are combined with ifosfamide. In previous studies, bleomycin has substituted for ifosfamide. However, after two lethal pulmonary toxicities occurred in young infants, ifosfamide was chosen but is withheld in young toddlers (Göbel et al. 2000). Up to four cycles of PEI are administered to high-risk patients. For patients with unresectable tumors that respond inadequately to up-front chemotherapy or relapse, a local therapy intensification with locoregional hyperthermia and thermochemotherapy is recommended (Wessalowski et al. 2003b).

One difficulty of establishing clear recommendations for treatment of pediatric germ cell tumors is the inability to define risk groups. Most trials are small and have

been conducted by individual national groups. Most pediatric trials combine different sites of origin, staging, and histology to the same stratum for therapy to achieve adequate statistical power. In contrast, for adult germ cell tumors, a large international meta-analysis has led to the introduction of a risk categorization that is currently used for the development and comparison of therapeutic trials (International-Germ-Cell-Cancer-Collaborative-Group 1997). A recent analysis of the US Children's Oncology Group has shown that this prognostic staging system, when adopted to a pediatric cohort, leads to a different stratification (Frazier et al. 2008). This is mainly explained by the different biology of germ cell tumors, in particular, during early childhood. Thus, the impact of high AFP levels has to be evaluated critically and under the consideration of yolk sac tumor being the only malignant histology in childhood.

Based on this consideration, an international attempt with a combined analysis of the US and British study registries has been taken to develop a new prognostic stratification system. Preliminary analyses show that a highly unfavorable risk group is defined for extragonadal, in particular, mediastinal germ cell tumors in adolescents. In fact, age emerges as a prognostic factor for mediastinal germ cell tumors. In line with the previous report from the German MAKEI study and the molecular genetic study (Schneider et al. 2002b), mediastinal nonseminomatous germ cell tumors of adolescents older than 10 years of age are prognostically unfavorable, whereas the corresponding tumors in young infants are not (Hale et al. 2010).

Specific recommendations for incorporating chemotherapy into the management of pediatric extragonadal germ cell tumors are discussed separately for each tumor. The dosages and methods of administration of current regimens employed in pediatric germ cell tumors [cisplatin, vinblastine, and bleomycin (PVB); cisplatin, etoposide, and bleomycin (PEB); and carboplatin, etoposide, and bleomycin (JEB)] are shown in Table 39.1.4 in Sect. 39.1.1.

It should be noted that complete initial resection with wide margins is rarely achieved in malignant extragonadal germ cell tumors. Therefore, apart from teratoma, only rare extragonadal malignant tumors are eligible for a watch-and-wait strategy. Patients with moderate-risk gonadal tumors or progression of disease in untreated tumors may be managed adequately with three to four cycles of a platinum-containing regimen. For higher-risk patients (higher-stage extragonadal tumors), four (to six) cycles of a platinum-based or dose-intensified chemotherapeutic regimen is indicated.

39.2.11 Treatment of SC-GCT

39.2.11.1 Sacrococcygeal Tumors

Sacrococcygeal germ cell tumors constitute the most frequent germ cell tumors during childhood and adolescence. In fact, sacrococcygeal teratoma is the overall most frequent neonatal tumor. The risk of malignancy increases with age. The surgical approach strongly depends on the anatomical site according to the Altman classification (Altman et al. 1974a). This classification categorizes tumors with regard to the extrapelvic (dorsal to the coccyx) and intrapelvic extension of the tumor. It is hypothesized that malignant tumors show a higher tendency to grow inside the pelvis. Although this classification is not consistently used, the basic consideration to evaluate preoperatively for intra- and extrapelvic tumor extension has a significant impact on surgical access and strategy.

39.2.11.2 Resection of Neonatal Sacrococcygeal Teratomas

Most neonatal teratomas, both immature and mature, present as large exophytic tumors that may be as large as the rest of the neonate. If the tumor is diagnosed with prenatal ultrasound, the child should not be delivered through vaginal delivery, since tumor rupture and severe hemorrhage may develop (Fig. 39.2.1). If the tumor is intact, there is no need for immediate resection, and preoperative imaging can be completed.

If the tumor has ruptured, then a pressure bandage may diminish the blood loss for a limited period of time. Prior to surgical resection, the degree of abdominal extension should be accurately evaluated if possible with US and MRI, to plan the approach.

The patient is usually positioned in the prone position, with a roll under the hips. Surgical principles that lead to a complete removal include a posterior approach with an inverted V shape to allow for excision of the tumor and to facilitate an eventually satisfactory cosmetic closure. This approach affords the surgeon excellent exposure for most neonatal sacrococcygeal germ cell tumors and may obviate the need for intra-abdominal exposures. The incision should be placed as

to preserve as much normal skin as possible: Excess skin can always be trimmed later if necessary.

Immature lesions are more vascular with significantly greater blood loss during surgery, and it is often necessary to perform blood transfusions (Altman et al. 1974a). The tumor is dissected from gluteus muscles, the coccyx is dissected at the sacrococcygeal joint, and the middle sacral vessels are controlled to minimize intraoperative hemorrhage. Failure to resect the complete coccyx is associated with increased risk of local recurrence (Göbel et al. 1997, 1998a).

The presacral extent of the tumor can compress the perineal structures forward; since the tumor may be adherent to the rectum, sharp dissection can be directed by placing a finger or a Hegar dilator in the rectum. The mass should be mobilized close to its pseudocapsule and removed, without spillage, en bloc with the coccyx. Then the anorectal and the retrorectal muscles are reconstructed. Closed suction drainage is adopted to evacuate fluid, and the wound is closed in layers.

If the tumor extends deeply through the bony pelvis into the retroperitoneum, an abdominal approach allows the mobilization of the mass and the control of the sacral artery. In some patients, a combined posterior and abdominal approach has to be chosen.

The tumor is eventually removed from the perineum. If the tumor has been ruptured and is actively bleeding, preliminary abdominal exploration is required: The aim is to find and ligate the middle sacral vessels; if this is not possible, an occlusive sling is placed across the aorta below the origin of the inferior mesenteric artery (Lindahl 1988).

Intraoperative hemorrhage and postoperative wound infections constitute the most frequent complications of excision of sacrococcygeal teratoma. The major cause of mortality is hemorrhagic shock, since an unsuspected teratoma may rupture during delivery. Neonatal teratomas need accurate clinical follow-up since local recurrences are observed in 4–20% of cases, in particular, if the coccyx is not removed. Of note, 50% of relapses are malignant (Fig. 39.2.7) (Göbel et al. 1998a). The infant should be followed with visits (including rectal examination), ultrasound, and AFP at 3-month intervals for at least 3 years and then annually. Recurrences rarely develop after the age of 2 years. The development of a malignant recurrence may be the result of an incomplete resection or a pathologic sampling error.

In a study from UK, the 5-year event-free survival for both mature and immature sacrococcygeal teratomas was approximately 75% (Mann et al. 2008a). Accordingly, the recurrence rate was 23% in 132 patients reported to the German MAKEI studies. Of note, the risk of malignant relapse with yolk sac tumor was minimized when postoperative chemotherapy was administered to patients with incomplete initial resection. However, the overall relapse rate was not reduced by chemotherapy (Göbel et al. 1998a). Cautious monitoring of such patients is required, because malignant germ cell tumors are well recognized to recur either from unnoticed malignant elements in the original tumor or from malignant transformation in residual tissue. Until recently, only a 10% salvage rate for malignant lesions was expected.

39.2.11.3 Resection of Malignant Sacrococcygeal Germ Cell Tumors in Toddlers

At the sacrococcygeal region, the risk of malignant germ cell tumor increases with age. However, even in neonates, malignant components may be detected histologically, the so-called yolk sac tumor microfoci (Harms and Jänig 1986). Therefore, accurate preoperative evaluation of the tumor markers and radiographic staging are necessary. The strategy for postoperative follow-up or adjuvant treatment and estimated prognosis is illustrated in Fig. 39.2.8.

Tumors are frequently non-capsulated and may develop in close proximity to the rectum. When invasion of the pelvic structures and/or extension into the spine are found or uncertain, the mass should be considered unresectable and a primary excision is discouraged. In these patients, an initial biopsy followed by neoadjuvant chemotherapy is the best choice (Göbel et al. 2000). Tumor shrinkage from platinum-based chemotherapy is highly successful and increases the achievement of complete resection with negative margins (Göbel et al. 2001).

Primary or delayed excision can be performed with posterior or combined (abdominal plus posterior) approach, depending on the site and extension of the tumor [according to Altman classification (Altman et al. 1974a)], and the surgical principles are the same, adopted for neonatal germ cell tumors, taking into consideration the crucial importance of a microscopically complete resection in patients with malignant lesions. The mass is removed with the coccyx, and multiple biopsies on the tumor bed should be performed to verify the completeness of the excision.

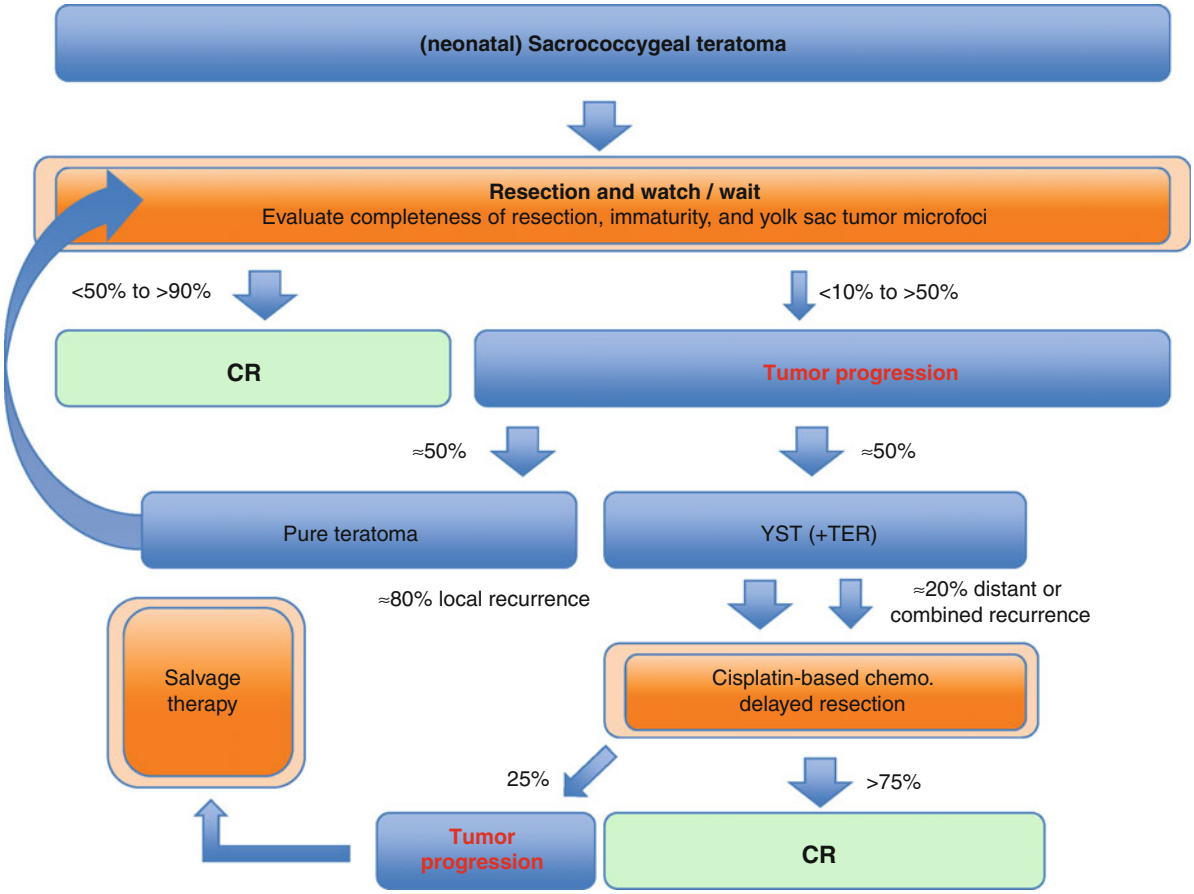

Fig. 39.2.7 Therapeutic algorithm in sacrococcygeal teratomas

Biopsy of suspected regional nodes (pelvic or inguinal) is recommended. If no residual disease is visible at imaging after neoadjuvant chemotherapy, coccygectomy is still required.

Surgery for extragonadal malignant germ cell tumors may be difficult due to the invasiveness of the tumor and the involvement of pelvic structures. Temporary colostomies may be required if rectal damages are caused during the resection. Neuropathic bladder or bowel disorders are reported in up to 30% of cases after major procedures (Rescorla 2008).

39.2.12 Surgical Resection of Intra- and Retroperitoneal Germ Cell Tumors

Compared to sacrococcygeal germ cell tumors, abdominal intra- or retroperitoneal germ cell tumors are rare and account for less than 5% of childhood germ cell tumors (Billmire et al. 2003) (Fig. 39.2.6). Histology and biology are comparable to other childhood germ cell tumors such as mediastinal tumors, with teratoma predominating in neonates and yolk sac tumors in toddlers. Mixed malignant germ cell tumors are observed in postpubertal patients. A testicular primary should always be excluded by clinical and ultrasound examination. In prepubertal patients, testicular biopsy is not recommended. However, it is often performed in postpubertal patients and in adults. Differential diagnosis is problematic, in particular, if the tumors are located in the upper retroperitoneum. In these tumors, the tumor marker AFP is equivocal, since other upper retroperitoneal tumors such as pancreatic tumors and metastases of hepatic tumors may also be associated with elevated AFP (Schneider et al. 2001e).

As for germ cell tumors arising at other sites, retroperitoneal germ cell tumors should also be resected in

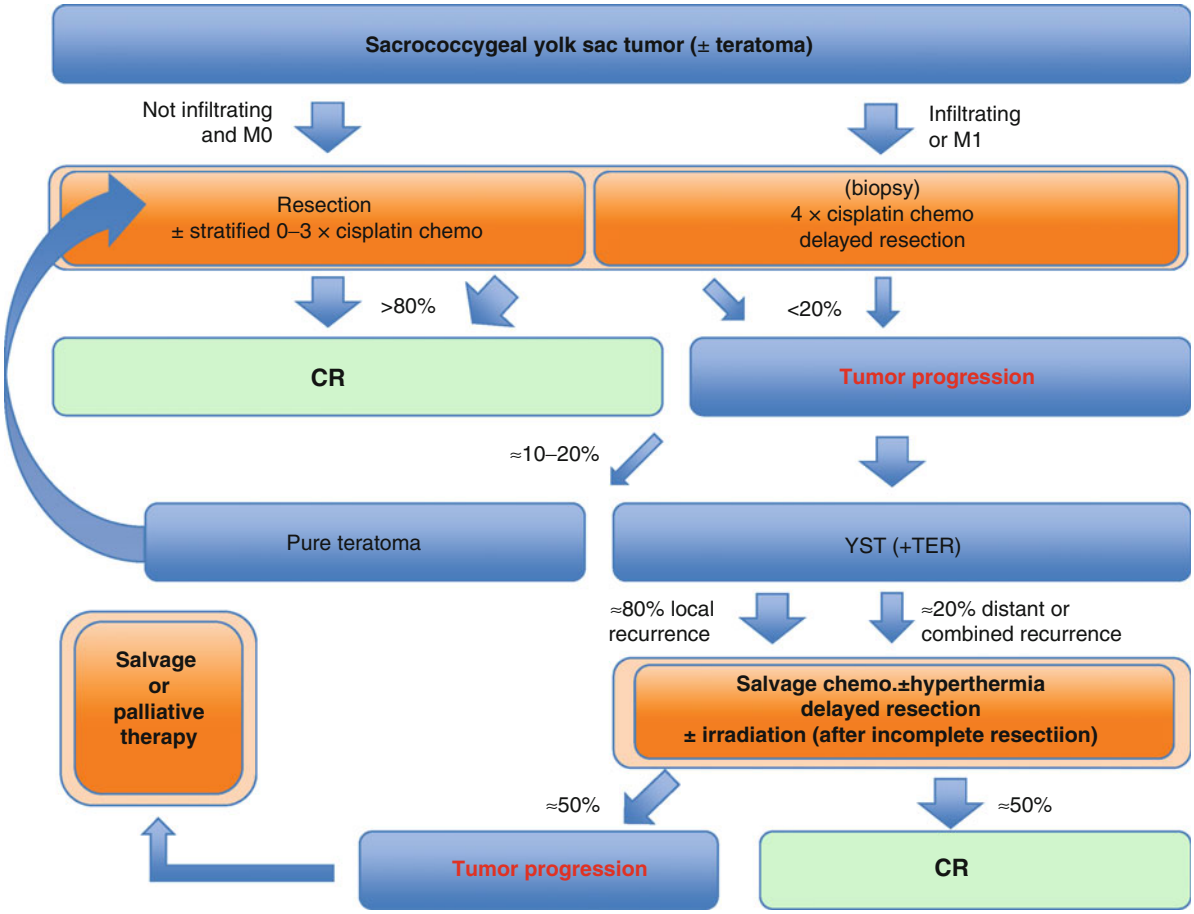

Fig. 39.2.8 Therapeutic algorithm in malignant sacrococcygeal yolk sac tumors

one piece and without spillage. In order to facilitate complete resection, a median laparotomy is chosen based on the anatomical situation of the tumor. Benign teratomas are usually well capsulated and not attached to retroperitoneal organs (Fig. 39.2.6). The excision represents the only therapy, and usually it is not difficult because they have a modest blood supply which is simply interrupted during the dissection. Adjacent lymph node should be sampled.

For large and invasive GCTs, the most important initial step is to establish the diagnosis clinically or with a biopsy, without performing extensive surgery. After neoadjuvant chemotherapy, mutilating surgery may be avoided in most cases.

Intraperitoneal GCT may be located in the liver or attached to the stomach or omentum. Gastric teratomas require the removal of a part of the gastric wall, which depend on the size of the tumor and the depth of the attachment (Billmire et al. 2003).

39.2.12.1 Surgical Resection of Vaginal Germ Cell Tumors

Although vaginal germ cell tumors are extraordinarily rare, they constitute a specific subgroup that is characterized by its limitation to yolk sac tumor histology in the absence of teratoma (Mauz-Körholz et al. 2000; Lopes et al. 1999). Moreover, these tumors show a low incidence of metastases. In the pre-platinum era, these tumors have been considered prognostically unfavorable, and extensive surgical resection including hysterectomy has been advocated. With the development of intensive platin-based combination chemotherapy, prognosis has dramatically improved. In fact, vaginal yolk sac tumors belong to the most curable subtypes of childhood germ cell tumors with a low relapse rate and excellent overall survival (Mauz-Körholz et al. 2000b). The prerequisite of this success has been the implementation of up-front chemotherapy, which usually induces excellent tumor response,

thus allowing for only limited resection on delayed surgery.

In most patients, enucleation of the pretreated tumor, often in combination with partial vaginectomy, is performed. In contrast to sacrococcygeal germ cell tumors, in which microscopically incomplete resection is associated with a high rate of local recurrences, microscopic residues obviously do not bear a dismal prognostic impact in vaginal yolk sac tumors.

Last, germ cell tumors may also rarely arise at other urogenital sites such as the penis or the prostate. In these tumors, complete surgical resection is considered a prerequisite of cure. In order to avoid mutilating surgery, a preoperative chemotherapy is recommended after initial diagnostic biopsy. The surgical strategy follows the general guidelines for oncologic surgery at the specific site.

39.2.12.2 Germ Cell Tumors of the Central Nervous System

Since CNS germ cell tumors are described extensively in this series' book on CNS tumors, only a brief description of the general therapeutic strategies is provided in this chapter.

As CNS germ cell tumors may develop at different, mostly midline sites, they may pose a significant challenge to the neurosurgeon (Figs. 39.2.4 and 39.2.5). In fact, large neonatal midline teratomas may be completely inassessable to treatment (Fig. 39.2.5). On the other hand, malignant germ cell tumors show a favorable response to chemotherapy and radiotherapy, in particular, in case of germinoma. Therefore, an initial surgical procedure should not be performed at the risk of provoking neurological damage or of sacrificing structures of vital importance such as vessels (Nicholson et al. 2002). Moreover, venous plexus may be in close neighborhood to, e.g., larger pineal tumors so that surgery may be complicated by hemorrhage. Last, surgical resection of hypophyseal tumors will lead to hypophyseal insufficiency with a lifelong need of hormone replacement.

In addition, it should always be considered in brain tumors that secreting germ cell tumors may easily be diagnosed based on serum and CSF tumor markers AFP and β-HCG. In patients with unequivocally elevated tumor markers, the clinical diagnosis may be established on markers and imaging even without surgical procedure and histologic confirmation. As a consequence, only a subset with marker of negative tumors requires histologic confirmation. The neurosurgical resection should be limited to initial (stereotactic, endoscopic, or open) biopsy. In patients with significant intracranial hypertension, biopsy may be combined with insertion of a ventricular-peritoneal drainage, or ventricular drainage can ideally be combined with biopsy during endoscopic surgery. There is no convincing evidence that aggressive surgical resection at diagnoses improves patients' oncologic prognosis, but there is considerably a concern that it may be associated with significant sequelae. Thus, many patients can be spared major brain surgery and can be cured with chemo- and/or radiotherapy.

The adjuvant chemo- and radiotherapy treatment heavily depends on histology and stage. Evidence of secreting tumor (AFP 25 μg/l and β-HCG 50 IU/μl) will lead to more intensive chemotherapy and higher radiotherapy doses. Evidence of (micro-) metastases on the cerebrospinal fluid will justify extended radiation fields including the cerebrospinal axis. Therefore, complete initial diagnostic assessment and staging constitutes the mainstay of treatment stratification. Moreover, the presence of diabetes insipidus has significant impact on infusion therapy during chemotherapy, since severe electrolyte imbalances may develop during hyperhydration required during platin chemotherapy.

Germinomas have traditionally been treated with radiotherapy, consisting of craniospinal irradiation with a tumor boost to 36 Gy (Bamberg et al. 1999). More recently, several studies from the US and Europe reported that both germinomas and secreting germ cell tumors can be successfully managed with a carboplatin-based chemotherapeutic regimen (Balmaceda et al. 1996; da Silva et al. 2010; Kellie et al. 2004; Khatua et al. 2010; Alapetite et al. 2002). However, omitting radiotherapy is associated with an increased risk of local recurrence. In analogy, the omission of craniospinal irradiation in patients receiving radiochemotherapy including focal irradiation is associated with an increased risk of ventricular recurrences (Alapetite et al. 2010). Therefore, the current international SIOP protocol will propose ventricular irradiation after carboplatin-based combination chemotherapy, in order to minimize this risk of ventricular relapse. For metastatic germinomas, craniospinal irradiation is proposed. The prognostic impact of residual tumor following chemo- and radiotherapy has to be considered carefully and in the context of the histology, in

particular, the presence of additional teratomatous components.

For secreting tumors, a combination of four cycles of cisplatin-based chemotherapy (PEI) supplemented by local (localized tumor) or craniospinal (metastatic tumors) irradiation with 45 Gy is recommended. In tumors with high AFP levels, chemotherapy is intensified with dose escalation of ifosfamide and etoposide.

39.2.13 Salvage Strategies

Therapy of malignant extragonadal germ cell tumors depends on histology at diagnosis and at relapse, site of recurrence, and first-line treatment (Figs. 39.2.7 and 39.2.8). In general, extragonadal germ cell tumors tend to recur at the primary tumor site. Nevertheless, prognosis of malignant extragonadal germ cell tumors that recur after platin-based chemotherapy is poor. This is primarily related to the fact that these tumors may develop resistance to chemotherapy (Mayer et al. 2003b). Second, the (surgical) chances to obtain a complete local control are usually significantly impaired at second-look surgery. Thus, scarring and changes in the normal anatomy after first surgery may impair surgical access to the recurrent tumor. Therefore, salvage strategy must always take both the local surgical situation and the general oncologic situation (metastases) into account. In general, salvage strategy must be planned and performed following an interdisciplinary approach.

The chances to successfully treat a malignant recurrence of a neonatal sacrococcygeal teratoma are good, in particular, if recurrence is detected at an early stage during regular follow-up. These tumors are usually treated with up-front cisplatin-based chemotherapy, followed by delayed tumor resection, which should be reserved to experienced pediatric surgeons (Fig. 39.2.7). If complete resection is obtained, the prognosis is comparable to that of primary sacrococcygeal yolk sac tumor.

In contrast, the outlook of recurrence after first-line chemotherapy is impaired. A switch, ideally an intensification of chemotherapy, is indicated in case of recurrence after first-line chemotherapy. In case of carboplatin-based first-line therapy, carboplatin can be replaced with cisplatin, and studies have shown that a substantial proportion of patients can be salvaged after the introduction of cisplatin (Baranzelli et al. 1999). Otherwise, salvage chemotherapy regimens in children including high-dose chemotherapy strategies are commonly derived from studies performed in adult patients. This experience is extensively reviewed in Sect. 39.1.1.

Ideally, a strategy should be developed that allows both to overcome resistance of tumor cells to chemotherapy and to facilitate local tumor control (Fig. 39.2.8). In this context, regional deep hyperthermia may provide promising aspects. Wessalowski and colleagues have treated children and adolescents with recurrent gonadal but mostly extragonadal germ cell tumors with cisplatin, etoposide, and ifosfamide in combination with regional deep hyperthermia (Wessalowski et al. 1997b, 2003b). The majority of patients were suffering from recurrent malignant sacrococcygeal germ cell tumors. Therapy was administered in a neoadjuvant strategy, with a delayed resection usually performed after the third or fourth cycles of thermochemotherapy. Of note, surgical resection was centralized to few experienced pediatric surgical centers, and in case of still incomplete resection, a proportion of patients additionally received local radiotherapy (Schneider et al. 2001e). With this approach, response to thermochemotherapy was favorable, as demonstrated by reduction of tumor size and decline of tumor markers. In addition, complete resection could be obtained in a proportion of patients, and in those not assessable to complete resection, radiotherapy appeared to enhance local tumor control additionally. With this strategy, a salvage rate almost comparable to that in first-line treatment was obtained – however, such favorable outcome was only achieved in patients referred to thermochemotherapy at first relapse. In later relapses, thermochemotherapy strategies are not as promising. This indicates that in case of relapse, early treatment intensification and stringent multimodal treatment strategies are an absolute prerequisite of cure (Schneider et al. 2001e). Unfortunately, thermochemotherapy is available only in few pediatric oncologic centers. Even more, any salvage strategy should nevertheless aim for the best possible tumor control. For this purpose, careful planning of surgical resection and, if required, radiotherapy is essential.

These considerations can be transferred to recurrent extragonadal germ cell tumors at any other site, including retroperitoneal, mediastinal, and vaginal germ cell tumors. For intracranial germ cell tumors, the same biologic and clinical observations can be made. They

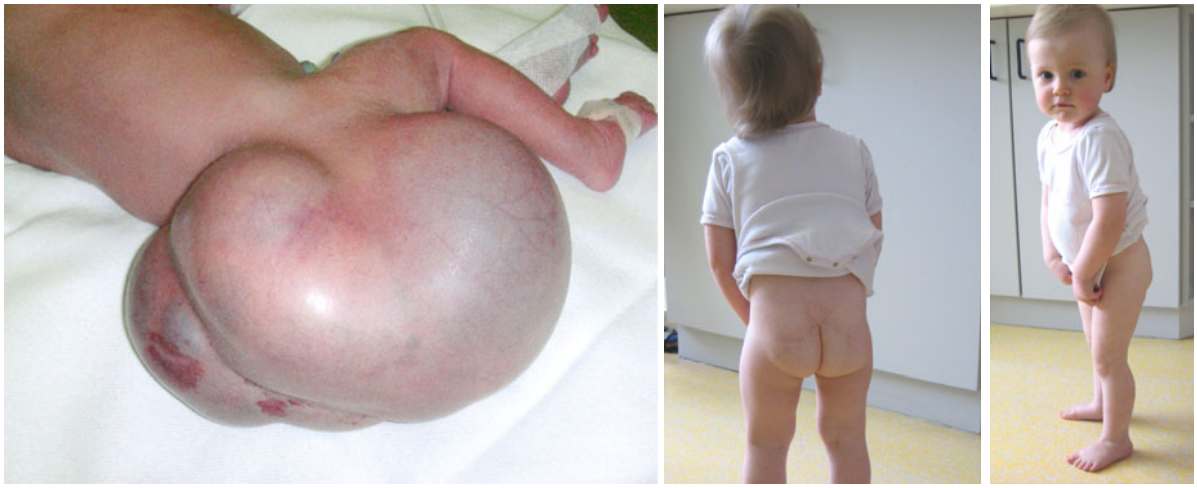

Fig. 39.2.9 Clinical presentation of a neonatal sacrococcygeal teratoma in a preterm girl delivered in the 32th week of pregnancy. The girl has become continent for both urine and stool at the age of 2 years

only rarely metastasize outside of the central nervous system. However, metastases within the ventricular system are not infrequent (Alapetite et al. 2010). In addition, local recurrences can be observed, in particular, in nonseminomatous germ cell tumors. Unfortunately, the chances to intensify local and systemic tumor control in recurrent central nervous system germ cell tumors are very restricted. Thus, most patients have been treated with intensive first-line chemotherapy. Only in case of carboplatin-based chemotherapy, a switch to cisplatin regimen opens the perspective to intensive chemotherapy significantly. If tumors recur outside of the radiation field, irradiation can be administered to these areas. However, it should be considered that usually such tumors present as metastatic tumors, thus requiring consolidating irradiation of the whole craniospinal axis. If high cumulative doses are required, toxicity may thus interfere with this approach. Thus, alternative strategies including intraventricular chemotherapy can also be administered, however, with currently only limited experience. Therefore, any salvage strategy in recurrent central nervous system germ cell tumors should be discussed with the respective study coordinator. Ideally, clinical data should be collected centrally in order to support the development of standardized and effective strategies including new irradiation techniques (e.g., protons), alternative chemotherapy strategies (e.g., high-dose chemotherapy), and alternative drugs (e.g., kinase inhibitors or antiangiogenetic drugs).

39.2.14 Prognosis and Late Effects

The prognosis of extragonadal teratomas is excellent if complete tumor resection is obtained. If tumor resection is incomplete, the risk of recurrence correlates with the grade of immaturity. Last, the recurrence risk also correlates with site, with incompletely resected sacrococcygeal teratomas being at the highest risk. Of note, half of recurrences present with malignant histology so that monitoring of AFP during follow-up is helpful in detecting these malignant relapses (Göbel et al. 1998a, b). It should be considered that despite the "benign" histology, teratomas are potentially lethal tumors. In a large series of 270 extracranial non-testicular teratomas, relapse rates of mature and immature teratoma were 10% and 18%, respectively. 25% of patients with tumor recurrence died, and almost half of the survivors underwent mutilating surgery with long-term sequelae such as palsy of the pelvic floor and incontinence (Göbel et al. 1998a). In contrast, the long-term outcome of patients who were successfully operated at initial diagnosis is favorable. Only a minority of patients with sacrococcygeal teratoma suffer from neurologic sequelae related to the tumor infiltrating the spinal canal, such as weakness of the lower limbs or incontinence, illustrated by the little girl of Fig. 39.2.9, who presented with a giant neonatal teratoma and was continent at the age of 2 years. Nevertheless, a proportion of patients may describe episodal or chronic constipation, which may rarely be significant (Draper et al. 2009).

The prognosis of teratomas at other extragonadal sites is comparably favorable and clearly exceeds 90% long-term survival (Göbel et al. 1998a; Marina et al. 1999b). Fortunately, the surgery-associated risks are tolerable, too. In head and neck teratomas, secondary hypothyroidism or parahypothyroidism has been reported (Bernbeck et al. 2009b).

A comparably favorable outcome has been reported for patients with malignant extragonadal yolk sac tumors. Certainly, vaginal yolk sac tumors appear to have the best overall prognosis with a cure rate exceeding 95%. This therapeutic success is the result of the exquisite chemotherapy sensitivity of these tumors so that even less-radical surgical procedures such as partial vaginectomy can be performed that may potentially lead to less long-term functional deficits (Lopes et al. 1999; Mauz-Körholz et al. 2000). In contrast, the prognosis of sacrococcygeal yolk sac tumors heavily depends on a radical surgical therapy with microscopically complete resection. If resection is incomplete, long-term outcome falls below 50%, whereas cure rates above 85% can be achieved after complete resection (Göbel et al. 2001). Accordingly, outcome is more favorable even in high-stage tumors if a neoadjuvant strategy with up-front chemotherapy and delayed resection is chosen, since at delayed resection a higher chance of complete resection can be obtained. Even if published experience is limited, there is no evidence that the cosmetic and functional outcome of malignant sacrococcygeal germ cell tumors is significantly different from that of sacrococcygeal teratomas. The most adverse indicator is invasion of the spinal canal and the sacral nerve plexus by the tumor, which may lead to pelvic palsy be it by the tumor or the surgeon (Draper et al. 2009).

Long-term toxicity related to chemotherapy is extensively discussed in Sect. 39.1.1. The same considerations can be taken into account for gonadal and extragonadal germ cell tumors.

39.3 Testicular Germ Cell Tumors

39.3.1 Introduction

Gonadal and extragonadal germ cell tumors (GCT) comprise approximately 2–3% of cancers diagnosed in children and adolescents younger than 15 years (Ries LAG et al. 1999b; Kaatsch 2004b). The survival of boys with testicular germ cell tumors has greatly improved with the application of lessons from adult GCT trials. However, significant differences exist between germ cell tumors from prepubertal boys and adolescents and young adults. Long-term toxicity may be a significant problem especially with treatment as a young child. We will explore the molecular basis of testicular germ cell tumor and risk-adaptive strategies that may be applicable to young boys and adolescents with malignant testicular germ cell tumors.

39.3.1.1 Testicular Germ Cell Tumors of Young Children – Genetics

In children younger than 4 years, germ cell tumors arising in gonadal and extragonadal sites are histologically, clinically, and genetically similar (for more details see Sect. 39.1.1). Most teratomas in this age group are diploid, have normal karyotypes, and, if completely resected, behave in a benign fashion regardless of degree of immaturity and site of origin (Kaplan et al. 1979b; Bussey et al. 1999b; Harms et al. 2006b). Malignant GCTs in prepubertal children are almost exclusively yolk sac tumors (Perlman et al. 1994b). Cytogenetic abnormalities involving chromosomes 1, 3, and 6 have been reported (Oosterhuis et al. 1988; Bussey et al. 1999b). In situ hybridization and loss of heterozygosity studies have demonstrated deletion of 1p36 in 80–100% of infantile malignant germ cell tumors arising from testicular and extragonadal sites (Stock et al. 1994; Sievers et al. 2005b).

39.3.1.2 Testicular Tumors in Adolescents and Adults – Genetics

Adolescent testicular germ cell tumors most commonly become clinically evident several years after puberty, suggesting that a critical genetic event occurs with, or is unmasked at, puberty. Germ cell tumors of the adolescent and adult testis demonstrate homogeneous genetic patterns including aneuploid DNA content and the isochromosome 12p or i (12p) (Oosterhuis et al. 1989; Atkin and Baker 1992; el-Naggar et al.

1992). Postpubertal testicular teratomas may have cytogenetic evidence of i (12p) and spread as a malignant GCT (Harms et al. 2006b).

The i (12p) can be found in 80% of postpubertal GCT and is comprised of two copies of the short arm of chromosome 12, fused at the centromere (Fig. 39.1.6 from gonadal chapter). Testicular tumors lacking i (12p) often show gain of 12p material within marker chromosomes (Rodriguez et al. 1993). The i (12p) has been documented by fluorescent in situ hybridization. This finding of i (12p) in intratubular germ cell neoplasia, a precursor lesion of testicular germ cell tumors, suggests that this genetic alteration occurs early in germ cell tumor pathogenesis (Looijenga et al. 1993). Testicular GCTs also have exhibited loss of chromosome 13 (38%), gain of chromosome 21 (45%), gain of chromosome 8 (45%), gain of chromosome 1q (36%), and high-level gain of 12p11.2–12.1 (Mostert et al. 1996). Other less frequent genetic changes have been noted. Adolescent testicular germ cell tumors, like normal embryonic germ cells, demonstrate biallelic expression of multiple imprinted genes including H19 and insulin-like growth factor-2 (van Gurp et al. 1994).

39.3.1.3 Pathology

Germ cell tumors comprise several histologic subtypes. The histologic features of each subtype are independent of presenting clinical characteristics. Both tumor biology and clinical behavior vary with site of origin, stage, and age of the patient (Altman et al. 1974b; Hawkins and Perlman 1996b). In contrast to mature teratomas which are almost always benign and diploid in infants or located in the ovary, the same histologic features are aneuploid and potentially malignant in the adult testis (Young and Scully 1990b). The histologic and pathologic classifications and descriptions have been previously described in Table 39.1.3 and Fig. 39.1.7 from gonadal chapter.

There are several points that are particular to testicular GCT. Teratomas and yolk sac tumors are the predominant histology prior to puberty. After puberty, other elements, seminoma, choriocarcinoma, and embryonal carcinoma are demonstrated. Pediatric immature teratomas primarily occur in extragonadal sites in children and in the ovaries of girls near puberty (Marina et al. 1999c). They are not usually present in the male testis. Yolk sac tumors (YST) are the most common pure malignant germ cell tumor in young children and are the most common GCT, benign or malignant, in the testes of infants and young boys (Young and Scully 1990b). Pure seminomas represent the most common malignant germ cell tumor in men older than 20 years. However, pure seminomas are unusual in men younger than 20 years. Embryonal carcinoma rarely occurs in a pure form in children and is more often a component of a mixed malignant germ cell tumor (Young and Scully 1990b; Hawkins and Perlman 1996b). This component is seen in adolescent testicular germ cell tumor (Fig. 39.1.7e, Sect. 39.1.1).

Table 39.3.1 Testicular germ cell tumor – presentation

– Teratoma	– Enlarging non-painful scrotal mass, surgery alone
– Volk sac tumor	– Most common pediatric GCT histology, enlarging non-painful scrotal mass
– Embryonal carcinoma	– More common in adolescents, may require more extensive surgery, similar presentation to above
– Mixed	– Less common in young males, combination of yolk sac tumor, embryonal carcinoma, and teratoma in postpubertal males
– Teratocarcinoma	– Adolescents
– Gonadoblastoma	– Bilateral 30%, poor sexual development
– Choriocarcinoma	– Rare, seen in mixed tumors, in adolescents, findings consistent with Klinefelter's

39.3.2 Clinical Diagnosis

The signs and symptoms of GCT are dependent on the site of origin of the tumor (Table 39.3.1). Pain especially is associated with testicular torsion (Giwercman et al. 1987). The absence of clinical findings often delays the diagnosis. Testicular GCTs present in two peaks during childhood and adolescence. The first peak is usually under age 4 years. Parents generally note these lesions, and patients may be brought to the attention of primary care physician in timely fashion (Fig. 39.3.1, left). Postpubertal males usually identify a mass but often delay reporting to their family or physician so that tumors are diagnosed at considerable size (Fig. 39.3.1, right). Perhaps this may also increase the risk for metastases. Diagnostic strategies specific

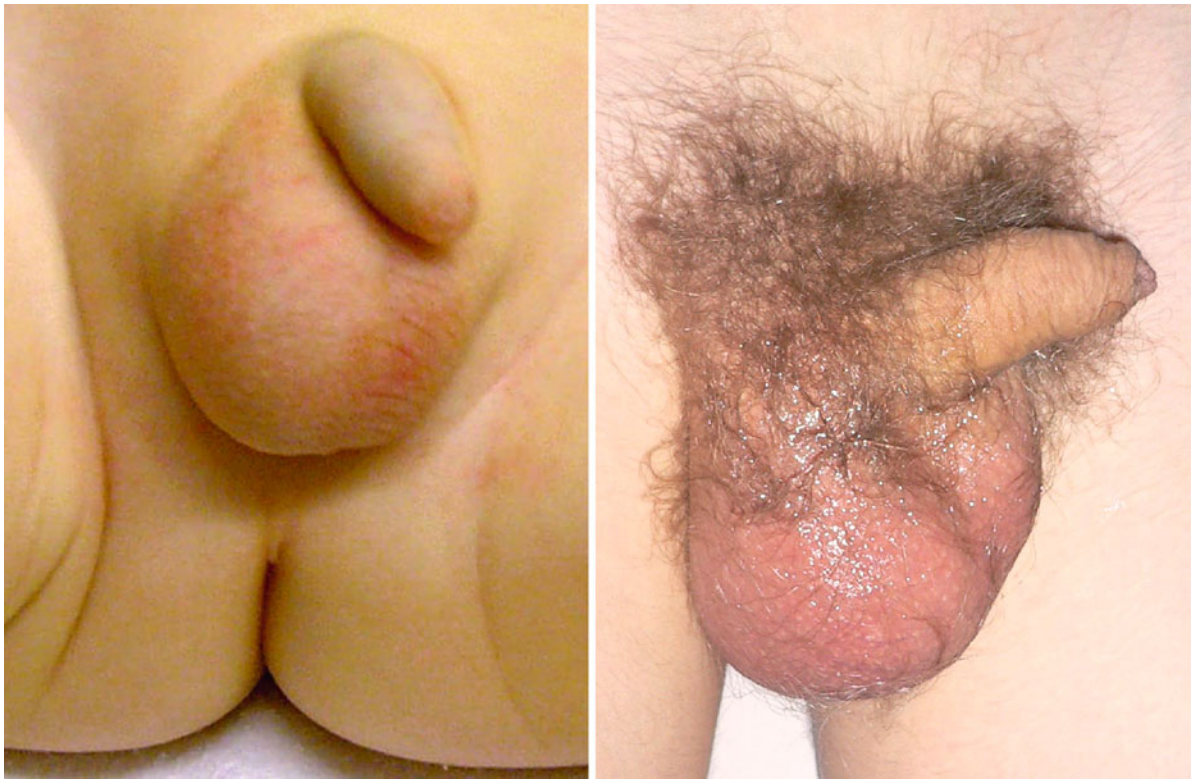

Fig. 39.3.1 Clinical presentation of testicular germ cell tumor in an infant (6 months old, immature teratoma + yolk sac tumor) and adolescent boy (15 years old, mixed malignant germ cell tumor with nodal metastases)

for testicular germ cell tumors are described in Table 39.3.2. A crucial point in the diagnosis and treatment of testicular GCT is referral to an appropriate surgeon. Testicular GCTs, in particular, in prepubertal children, can often be treated with surgery and observation. If the wrong surgical approach is taken, the patient may require chemotherapy. This will be discussed further in treatment section.

39.3.3 Staging

Staging of testicular germ cell tumors is closely linked to treatment. An improper diagnostic procedure, for example, a trans-scrotal biopsy with contamination, will upstage a patient. This patient will then require chemotherapy. Table 39.3.3 shows the clinical surgical staging system as defined by intergroup pediatric trials from the US. Ideally, patients with testicular masses should have appropriate imaging and marker studies prior to diagnostic biopsy or orchiectomy.

Several features must be considered in stage I testicular germ cell tumor. The surgical approach may determine stage and need for further treatment. An inguinal approach with high ligation of spermatic cord and vessels may ensure complete resection and classification of stage I disease. An additional feature is marker decay. Most prepubertal males have yolk sac tumor with elevated AFP as the predominant histology. An appropriate AFP decline (half-life, 5–7 days) would confirm stage I disease. An AFP that does not return to normal or rises would suggest stage II disease in the absence of positive imaging. This patient would need to be treated with chemotherapy. The prognosis is excellent for stage I with approximately 70% of patients requiring no chemotherapy. The remaining patients can usually be salvaged with standard cisplatin chemotherapy. The treatment of postpubertal males must be informed by adult GCT studies, which will incorporate histology (embryonal carcinoma associated with a worse prognosis) and vascular invasion. Testicular germ cell tumors have a

Table 39.3.2 Specific diagnostic strategy in testicular GCT

Procedure	Specific questions
Clinical assessment	
Phys. examination	Non-tender testicular mass, suspected torsion of testis, undescended testis, Klinefelter's syndrome
Laboratory assessment	
– AFP (β-HCG)	Malignant GCT with yolk sac tumor – consider age-related reference range (or choriocarcinoma)
– LDH	May be prognostic in older males
Radiographic assessment	
Chest, abdomen, pelvis – CT scan	Most common sites of metastatic spread from testis are retroperitoneal lymph nodes and lungs
Testicular ultrasound	Examine both testes (bilateral cases possible)
Bone scan	Not usually required in young boys but may need evaluation in older males
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)
(β-HCG)	Exclusion of choriocarcinoma
(CD-30)	Exclusion of embryonal carcinoma
(OCT3/4)	Exclusion of seminoma (embryonal carcinoma)

Table 39.3.3 Testicular germ cell tumor – staging

I	Complete resection. Disease limited to testis. Surgical approach – high inguinal ligation or trans-scrotal (with no spillage). No evidence of metastases. Appropriate marker decline
II	Microscopic disease in scrotum or spermatic cord (≤5 cm from proximal end). Trans-scrotal with spillage
III	Retroperitoneal involvement (>2 cm sized nodes) or biopsy positive
IV	Metastatic

propensity to metastasize to retroperitoneal lymph nodes. Postpubertal males, in particular, often have residual teratomatous material that has the potential to dedifferentiate later into malignant disease. For this reason, many physicians, treating adult patients with GCT, recommend removal of residual tissue. Figure 39.3.2 demonstrates the full extent of nodal metastases from an initial testicular primary. A mixed YST and embryonal carcinoma spread to retroperitoneal nodes, posterior mediastinal nodes, and eventually to left supraclavicular nodes. The last finding brought patient to medical attention, as the testicular primary was small.

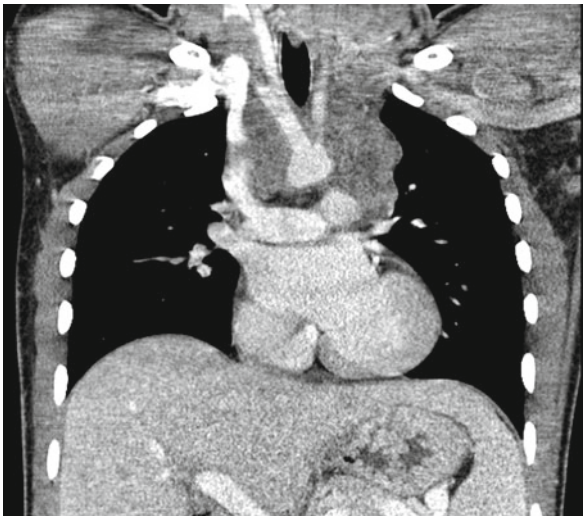

Fig. 39.3.2 Testicular germ cell tumor with YST and embryonal carcinoma histology metastatic throughout retroperitoneal and posterior mediastinal lymph nodes to supraclavicular nodes

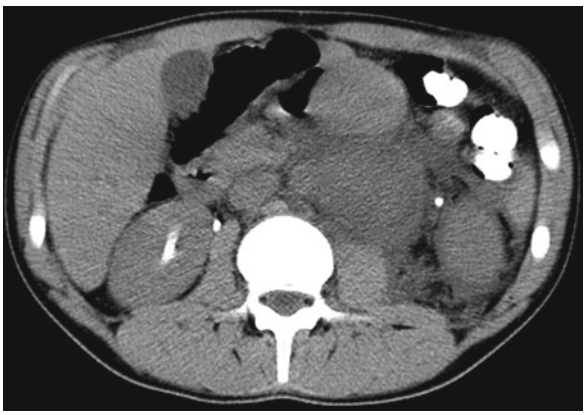

Fig. 39.3.3 Recurrent retroperitoneal seminoma, 4 years after surgery for stage I seminoma

The question of retroperitoneal lymph node dissection for accurate staging of testicular GCT has been long standing and complex. In boys less than 4 years of age, there are no data to suggest that this surgical approach is warranted. The outcome, even in stage IV, is excellent, and residual teratoma is not usually present. In adolescent males, this is still an important question. Figure 39.3.3 shows recurrence of seminoma in an adolescent who did not have RPLND or return for observational studies.

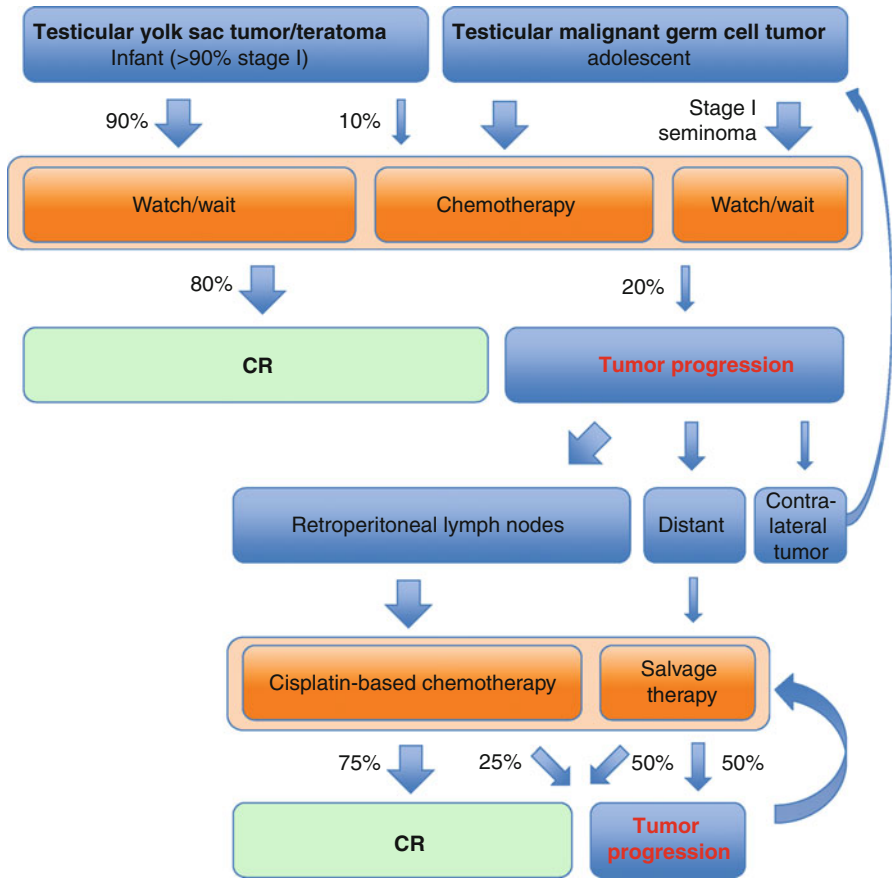

Fig. 39.3.4 Treatment algorithm for malignant testicular GCT

39.3.4 Therapy

An individualized, multimodality treatment plan is necessary due to the heterogeneity of pediatric germ cell tumors relative to site of origin, age, histology, and stage. Different subsets have been being described for childhood and adolescent germ cell tumors (Schneider et al. 2004c). Most patients are referred after orchiectomy, and treatment will be directed based on staging. In the US, the Children's Oncology Group staging for testicular GCT reflects other pediatric tumors. The advent of effective chemotherapy may mitigate the need for initial extensive surgery. Figure 39.3.4 details practical options in the treatment of testicular germ cell tumors.

Surgery represents the cornerstone of the management of testicular GCT. Generally, a primary complete excision is feasible. Protocols recommend an inguinal approach with vascular control before mobilization of the testis (Schmidt et al. 2002a; Lo Curto et al. 2003). If a malignant GCT is confirmed by frozen section examination of the mass, en bloc resection of testis and spermatic structures with ligation of the cord at the inguinal ring is required (Schlatter et al. 2003). Patients with scrotal skin involvement and those operated or biopsied through a scrotal approach should undergo a hemiscrotectomy to ensure local control. Some authors state that this procedure can be avoided if patient is upstaged from stage I to stage II and receives chemotherapy (Billmire 2006a). Primary retroperitoneal lymph node dissection (RPLND) is not indicated in prepubertal boys, since malignant GCTs are highly responsive to chemotherapy (Haas et al. 1999). Limited biopsy may be necessary to define staging when the involvement of retroperitoneal lymph nodes is uncertain after imaging. However, RPLND may be necessary when enlarged nodes remain after chemotherapy. Inguinal node exploration is indicated only in patients with scrotal involvement.

Patients with completely resected testicular GCT do not require chemotherapy. The "watch-and-wait" approach requires scheduled serial physical examination, tumor marker determination, and primary tumor imaging to ensure that a recurrent tumor is detected without delay. A discussion of tumor marker is warranted, especially in

testicular stage I germ cell tumor. Tumor markers, especially AFP in prepubertal male, must fall according to AFP half-life. While it is usually 5–7 days, some patients will have longer half-life. The failure to normalize or any significant rise in AFP suggests the presence of residual tumor, and patient should receive chemotherapy even without imaging or biopsy confirmation. In a few cases AFP can show minimal rise and fall secondary to other causes. Many investigators agree that in this population, five times the upper limit or normal is too high.

The prognosis of GCT has improved significantly with the development of cisplatin-based therapy in adult testicular GCT patients (DFS 68–92%) (Einhorn and Donohue 1977b; Ozols et al. 1988; Einhorn et al. 1989b). Prior to this effective chemotherapy, children with extracranial malignant germ cell tumors (GCT) had 3-year survival rates of 15–20% with surgery and radiation therapy (Kurman and Norris 1976b). However, boys with localized testicular tumors do well with surgical resection (Schlatter et al. 2003). Prognosis and appropriate treatment depend on factors such as histology (e.g., seminomatous vs. nonseminomatous), age (young children vs. adolescents), stage of disease, and primary site (Baranzelli et al. 1999c; Marina et al. 2006b). Children with extracranial malignant GCT should be cared for at pediatric cancer centers with experience treating these rare tumors, to maximize the likelihood of long-term survival while minimizing the likelihood of treatment-related long-term sequelae (e.g., secondary leukemias, infertility, hearing loss, renal dysfunction).

Cisplatin-based chemotherapy has dramatically improved the outcome for children with extracranial GCT, with 5-year survival rates of more than 90% (Mann et al. 2000c; Göbel et al. 2002a; Cushing et al. 2004c; Rogers et al. 2004c). Chemotherapy strategies developed by various international pediatric germ cell tumor committees were previously described in Table 39.1.6 (gonadal chapter). The standard chemotherapy regimen for both adults and children with malignant nonseminomatous GCT includes cisplatin, etoposide, and bleomycin (PEB), though children receive fewer doses of bleomycin than adults. The combination of carboplatin, etoposide, and bleomycin (JEB) has undergone clinical investigation in the United Kingdom in children younger than 16 years and is reported to have a similar event-free survival (EFS) by site and stage as PEB (Mann et al. 2000c). It must be noted that these were not randomized trials. The use of JEB appears to be associated with less ototoxicity and nephrotoxicity than PEB.

In an intergroup study conducted by the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG), the benefit of increasing the dose of cisplatin [high-dose (HD)-PEB: 200 mg/m^2 vs. PEB: 100 mg/m^2 of cisplatin] was studied in a randomized manner in patients with extragonadal and advanced gonadal GCT (Cushing et al. 2004c). Intensification of cisplatin in the HD-PEB regimen provided some improvement in EFS; however, the use of HD-PEB was associated with a significantly higher incidence and severity of ototoxicity and nephrotoxicity. In a subsequent study, amifostine was not effective in preventing hearing loss in patients who received HD-PEB (Marina et al. 2005).

Other groups (Germany, Brazil, France) have studied the omission of bleomycin from front-line therapies. Regimens without bleomycin were developed for favorable-risk germ cell tumors. Excellent outcomes were maintained.

The treatment of testicular GCT in adolescents and adults has been informed by a large meta-analysis study. Postpubertal males with testicular GCT should be treated according to these guidelines (Group 1997b).

There are several points that should be made concerning treatment approaches in patients with testicular germ cell tumors containing specific benign or malignant elements.

39.3.4.1 Teratoma

Immature teratomas are rarely found in the prepubertal testis. Teratomas, in prepubertal males, almost always take a favorable clinical course. Surgery is the treatment for these patients and all patients with such benign teratomas. Inguinal orchiectomy is usually required for mature and immature GCT (Mann et al. 2008b). However, testis-sparing procedure through the inguinal canal may be considered when markers and investigations suggest a benign process. The feasibility of a conservative resection (tumorectomy) depends on size and location. Re-excision may be necessary for residual tumor. Inguinal orchiectomy may be required for mature and immature germ cell tumors (Mann et al. 2008b). The postpubertal adolescent patient with a germ cell tumor presents additional challenges. Residual teratomatous material has been associated with significant malignant GCT recurrence within 10 years. Therefore, several institutions advocate resection of all residual material in postpubertal males. This may include RPLND (Carver et al. 2005, 2007d).

39.3.4.2 Seminoma

Seminomas of the testis are almost exclusive to the postpubertal male. Seminomas display an outstanding response to treatment, both chemotherapy and radiation therapy. In most patients, residual tumor after chemotherapy is resected. Nevertheless, the therapeutic impact of tumor resection in highly regressive tumors is controversial. In these instances, post-chemotherapy PET assessment may assist in decision making. Any PET positive tumors should be resected irrespective of size. In contrast, PET negative tumors smaller than 1–2 cm can be followed, whereas larger tumors should also be excised. In unresectable viable seminomas, irradiation constitutes a promising salvage therapy. However, it is not recommended for first-line therapy, since the long-term side effects associated with mediastinal irradiations may be significant. Patients with stage I seminomas must be observed carefully for at least 5 years, as late retroperitoneal recurrence is possible (Fig. 39.3.3).

39.3.4.3 Embryonal Carcinoma

Embryonal carcinoma is usually seen in postpubertal males with testicular germ cell tumors as part of a mixed tumor. In postpubertal males, an increased percentage of embryonal carcinoma histology in a mixed tumor correlates with worse prognosis and possibly suggests a need for chemotherapy. The infrequent incidence of this histology in prepubertal males makes conclusions difficult.

39.3.5 Prognosis

Patients with mature and immature teratomas will have an EFS of near 100% with surgery alone (Mann et al. 2008b).With a multidisciplinary approach, boys with malignant testicular GCT have an outstanding prognosis. In the US intergroup studies, boys (pre- and postpubertal) with stage I, II, and III testicular GCT had an overall survival rate of 100% (Schlatter et al. 2003; Cushing et al. 2004c; Rogers et al. 2004c). Other pediatric groups have reported similar results (Göbel et al. 1990; Baranzelli and Patte 1998; Mann et al. 2000c; Göbel et al. 2002a; Lopes et al. 2009b). The US trial included boys up to age 18 years. Overall survival rates for boys <15 and >15 years were 100% and 84%, respectively (Cushing et al. 2004c). It must be noted that most of the boys >15 had pure yolk sac histology.

39.4 Germ Cell Tumors of the Ovary

39.4.1 Introduction

The general aspects of germ cell tumors (GCTs) common to all GCTs occurring at different sites have been previously discussed in general gonadal chapter. Ovarian tumors are rare, accounting for only about 1% of childhood malignancies (Bernstein et al. 1999). The incidence increases after 8 years and peaks at 19 years. Ovarian GCT development parallels gonadotropin release (Cronen and Nagaraj 1988; Walker et al. 1988; dos Santos Silva and Swerdlow 1991). In contrast to adult ovarian tumors, most pediatric ovarian tumors are of germ cell origin. Few children present with tumors of epithelial and stromal origin, as seen in adult patients (Lovvorn et al. 1998). Approximately 5% of ovarian germ cell tumors develop bilaterally. Thus, bilateral tumors may be present at diagnosis (synchronous manifestation) or develop during follow-up (metachronous manifestation).

39.4.2 Ovarian Tumors GCT in Adolescents and Adults – Genetics

The genetic biology of ovarian germ cell tumors is more complex than that of testicular germ cell tumors and is considered separately for mature teratomas, immature teratomas, and malignant ovarian germ cell tumors. There is a considerable association with sex-chromosomal abnormalities such as Ullrich-Turner syndrome and testicular feminization (Sect. 39.1.1).

39.4.2.1 Teratomas

Mature teratomas demonstrate karyotypically balanced cytogenetics (95%), with only 5% showing gains of single whole chromosomes (Parrington et al. 1984; Surti et al. 1990). Characteristically, they may show an isodisomic karyotype (23,X ×2). A methylation profile of imprinted genes (e.g., hypermethylation of SNRPN), also consistent with a postmeiotic origin, is often seen in ovarian teratomas (Schneider et al. 2001g).

39.4.2.2 Immature Teratomas

Ovarian immature teratomas are heterogeneous with evidence of a meiotic stem cell origin or mitotic origins. This suggests failure of early meiotic arrest (Ohama et al. 1985). Immature and mature teratomas may represent different biologic entities, rather than simply a

spectrum of maturation. Chromosomal abnormalities are more common in immature teratoma. Patients with cytogenetically abnormal immature teratomas often develop recurrence. In contrast, patients with karyotypically normal immature teratomas do not (Ohama et al. 1985; King et al. 1990; Gibas et al. 1993).

39.4.2.3 Malignant Ovarian Germ Cell Tumors

Malignant ovarian GCTs in postpubertal girls have similar genetic findings when compared to testicular malignant GCTs, including presence of i (12p) (75%), gains of chromosomes 21 and 1q (42% and 32% respectively), and loss of chromosomes 13 and 8 (25% and 42% respectively) (Speleman et al. 1990; Hoffner et al. 1994; Thompson et al. 1994; Riopel et al. 1998). Although malignant ovarian germ cell tumors appear to be equivalent to their adolescent testicular counterparts, immature and mature ovarian teratomas remain as unique subcategories of germ cell tumors likely to have a different mechanism of origin.

39.4.3 Histopathology

Pathologic characteristics are described in Sect. 39.1.1. The majority of ovarian germ cell tumors are either mature teratomas or immature teratomas. Significant distribution differences do not exist in pre- and postpubertal females. Yolk sac tumor is the most common malignant element seen in mixed germ cell tumors. It is usually associated with immature teratoma.

39.4.4 Clinical Diagnosis

Clinical features of ovarian germ cell tumors are detailed in Table 39.4.1. Abdominal pain is the most common presenting symptom (80%) (Cronen and Nagaraj 1988; Gribbon et al. 1992; Lovvorn et al. 1998). The pain is usually chronic but some patients present with an acute abdomen, often secondary to torsion. Other signs and symptoms include a palpable or even visible abdominal mass (Fig. 39.4.1), abdominal distension, fever, constipation, amenorrhea, vaginal bleeding, and rarely frequency and dysuria (Harris and Boles 1974; Lovvorn et al. 1998). Precocious puberty can be seen in most malignant GCT, though it is more frequent in ovarian sex cord stromal tumors. AFP levels are increased in patients with yolk sac tumors.

Table 39.4.1 Ovarian cell tumor – presentation

– Teratoma Mature Immature	Palpable mass, abdominal pain 15%, bilateral Implants
– Dysgerminoma	Pain, rapid growth, ovarian torsion
– Yolk sac tumor	Pain, mass, torsion
– Embryonal carcinoma	Rare, precocious puberty
– Choriocarcinoma	Part of mixed tumor
– Mixed germ cell tumor	30% precocious puberty
– Gonadoblastoma	Dysgenetic ovaries, bilateral

Mixed ovarian germ cell tumors with elevated AFP are usually composed of immature teratoma and varying amounts of yolk sac elements. Specific diagnostic strategies for ovarian tumors are described in Table 39.4.2.

39.4.5 Staging

Ultrasound is most often used for the initial evaluation of patients with abdominal or pelvic masses and will differentiate cystic from solid masses (Surratt and Siegel 1991). Although the presence of a solid ovarian mass raises the suspicion of malignancy, the majority are benign teratomas (Cronen and Nagaraj 1988). Computed tomography (CT) is helpful in identifying the site of origin, the extent of tumor, the presence of calcifications or fat, and metastatic disease. Many children with teratomas do not have evidence of fat on CT scan (Jabra et al. 1993). Neuroglial implants, containing mature or immature teratomatous elements, may be identified. They do not usually affect prognosis. Figures 39.4.2–39.4.4 show CT findings of ovarian teratoma, yolk sac tumor, and dysgerminoma, respectively, illustrating that tumors are hardly distinguishable by imaging. Staging evaluation should include a chest CT and bone scan, though metastases to bones are rare. Central nervous system metastasis is unusual, and routine imaging of central nervous system is not indicated.

Serum tumor markers AFP and β-HCG are essential because the majority of pediatric patients with ovarian germ cell tumors have a yolk sac tumor component, and mixed malignant germ cell tumors may also include significant choriocarcinoma components (Mann et al. 1989b; Marina et al. 1992).

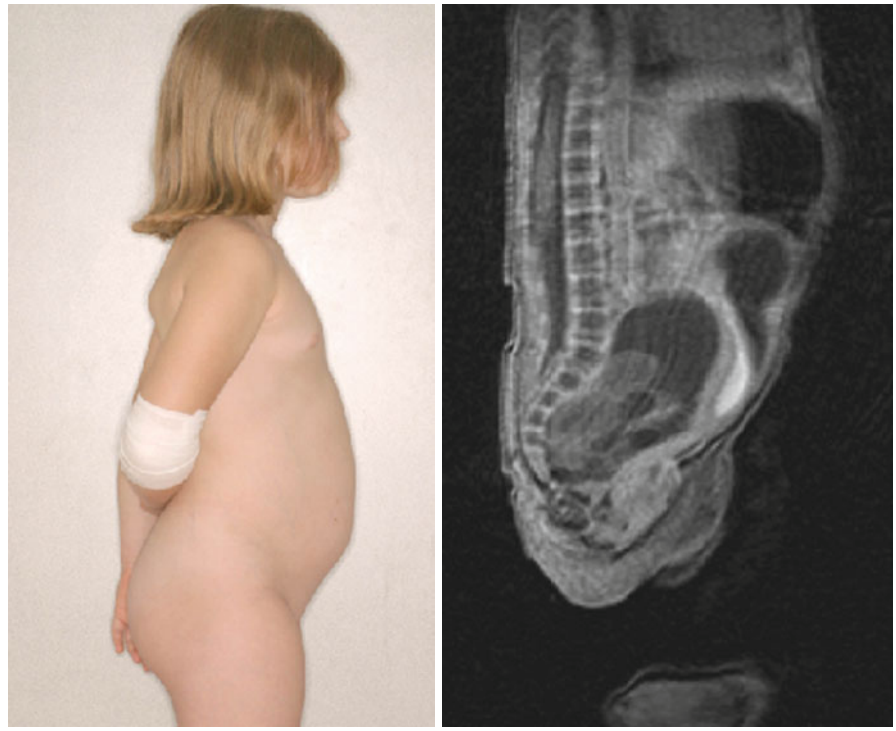

Fig. 39.4.1 11 year old girl presenting with a large abdominal teratoma

Table 39.4.2 Specific diagnostic strategy in ovarian tumors

Procedure	Specific questions
Clinical assessment	
Phys. examination	Abdominal pain (acute or chronic), rapidly developing abdominal mass, sexual precocious
Laboratory assessment	
– AFP (β-HCG)	Malignant GCT with yolk sac tumor – consider age-related reference range (or choriocarcinoma)
– Catecholamines	Exclusion of neuroblastoma
– LDH	May have prognostic significance
Radiographic assessment	
Abdominal ultrasound	Examination of both ovaries, presence of cysts or solid components
CT chest, abdomen, pelvis	Site, size, organ of origin, cystic structures, calcification, metastases
Bone scan	Rare
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)
(β-HCG)	Exclusion of choriocarcinoma
(CD-30)	Exclusion of embryonal carcinoma
(OCT3/4)	Exclusion of dysgerminoma (embryonal carcinoma)

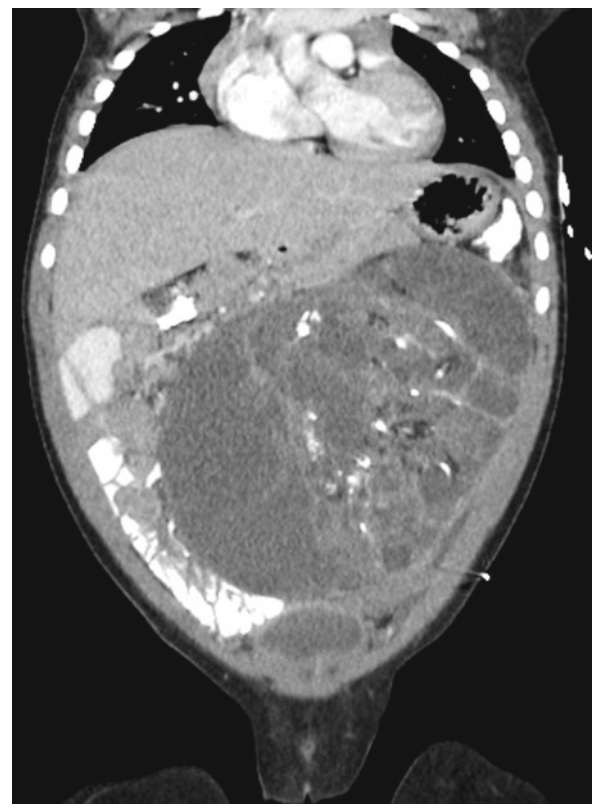

Fig. 39.4.2 Ovarian teratoma in a 2 year old

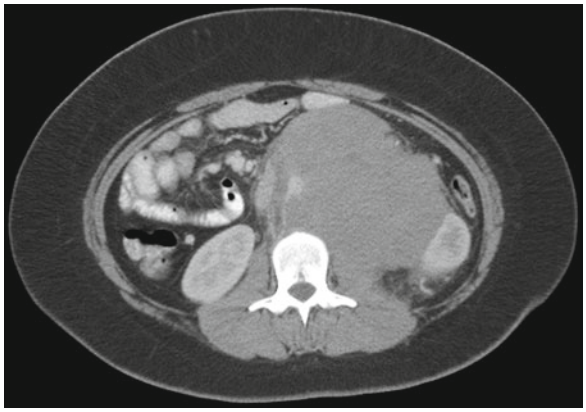

Fig. 39.4.3 Large ovarian yolk sac tumor involving retroperitoneal nodes. After chemotherapy, second surgery revealed only scar and no residual tumor

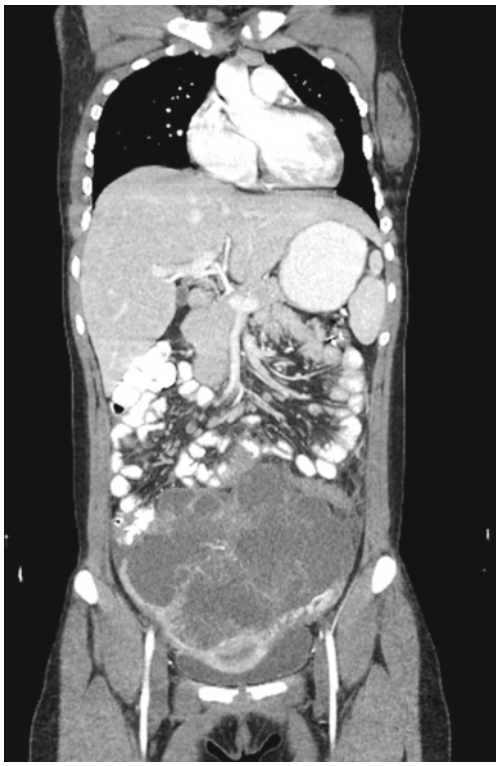

Fig. 39.4.4 Large ovarian dysgerminoma in adolescent

Staging systems modeled after the by FIGO system (Table 39.4.3) may be the most useful because different strategies must be followed for different histologies (Cannistra 1993). This system includes cytological examination of any thoracic or peritoneal fluid. The FIGO staging system has been used in several international pediatric germ cell studies. The US intergroup study used a surgicopathologic system to refine the FIGO system. In the US staging system, strict guidelines are required for an ovarian tumor to be categorized as stage I. Unless all surgical guidelines are followed or in the event of peritoneal contamination, such as seen in rupture, the patient will be upstaged to stage III and receive chemotherapy. If chemotherapy is to be administered for any ovarian germ cell tumor, the FIGO staging system is not necessary.

Table 39.4.3 Ovarian germ cell tumor – staging according to FIGO

Stage	Extent of disease	
I		Limited to the ovaries
	Ia	To one ovary, no ascites. No tumor on external surface, capsule intact
	Ib	Both ovaries, no ascites. No tumor on external surface, capsule intact
	Ic	One or both ovaries but with tumor on surface of one or both ovaries, or capsule ruptured, or positive ascites or positive peritoneal washings
II		Tumor involving one or both ovaries with pelvic extension
	IIa	Extension and/or metastases to uterus and/or tubes only
	IIb	Extension to other pelvic tissues
	IIc	As in IIa or IIb but with positive ascites or positive peritoneal washings, or with capsule ruptured
III		Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal lymph nodes, extension to small bowel or omentum, superficial liver metastases
	IIIa	Limited to true pelvis grossly with negative nodes but histologically confirmed microscopic seeding of abdominal peritoneal surfaces
	IIIb	Limited to one or both ovaries with negative nodes but histologically confirmed implants of abdominal peritoneal surfaces, not < 2 cm diameter
	IIIc	Abdominal implants >2 cm diameter and/or positive retroperitoneal or inguinal nodes
IV		Tumor of one or both ovaries with distant metastases outside of peritoneal cavity, parenchymal liver metastases; pleural effusion, if present, must have positive cytology

39.4.6 Therapy

The background for treatment of ovarian GCT can be informed from previous discussions in general gonadal chapter. There are features that are unique to ovarian tumors. Most recommendations relate to surgical options based on distinct histology. Surgery has a prominent role in the treatment of patients with ovarian tumors. However, since malignant germ cell tumors are very chemosensitive, primary excision should be attempted only when the surgeon thinks a complete resection can be obtained without a mutilating procedure (Billmire et al. 2004b; Billmire 2006b). If imaging shows invasion of other structures (i.e., bladder, uterus, vagina) or bilateral ovarian involvement, a tumor biopsy is the best option. The biopsy may be "open" or with a tru-cut needle. Under ultrasound guidance, multiple biopsies should be obtained from different sites for histologic diagnosis and collection of material for biology studies. If AFP and β-HCG are elevated, biopsy may not be necessary. After neoadjuvant chemotherapy, the patient will undergo delayed surgery.

Primary excision of ovarian tumors can be approached from a Pfannenstiel incision, an infraumbilical transverse incision or a midline approach. Since malignant tumors and benign tumors cannot be distinguished based on gross features alone, all tumors should be staged according to current staging principles (Göbel et al. 1998d; Billmire 2006b).

- Aspiration of ascitis, if present, or peritoneal washing for histology.
- Examination of omentum and removal of suspected nodules.
- Inspection of peritoneum and abdominal organs, with biopsy of abnormal areas. Peritoneal implants (gliomatosis peritonei) may be associated with mature and immature teratomas.
- Examination and palpation of contralateral ovary with biopsy of suspicious areas.
- Complete removal of involved ovary, avoiding spillage. Ipsilateral fallopian tube may be spared if not adherent to mass.
- Inspection of iliac and aorto-caval nodes with biopsy of suspicious nodes.

Laparoscopy is usually discouraged for removal of malignant tumors, as the violation of capsule or rupture can result in upstaging the tumor. Secondary excision should be done if the initial approach was a biopsy followed by chemotherapy (Schmidt et al. 2002b). Most authors recommend a conservative approach for bilateral tumors (if possible on least affected side) to preserve ovarian function. Bilateral oophorectomies and other extensive surgeries should be reserved when tumors do not respond to chemotherapy.

Special mention should be made concerning ovarian torsion. Approximately 10% of ovarian tumors present as acute abdomen secondary to torsion or rupture of tumor. Most ovarian masses associated with torsion are benign (Pienkowski et al. 2004). Ovarian torsion is an emergency and laparoscopy is preferred. If a tumor is suspected, immediate oophorectomy should be done. If a mass is found incidentally, a thorough abdominal inspection must be done (Hayes-Jordan 2005).

39.4.6.1 Teratoma and Immature Teratoma

The majority of ovarian germ cell tumors are either mature teratomas or immature teratomas. In the first months of life, most ovarian tumors are benign (Bagolan et al. 1992). Most teratomas (but also some mixed malignant germ cell tumors) are cystic and may present with considerable size (Fig. 39.4.5). Surgery is the treatment of choice, whether or not they contain malignant elements (Templeman and Fallat 2005). The procedure often requires oophorectomy due to size and pathologic uncertainty. However, in selected case, tumor enucleation may be possible. Every effort should be made to preserve hormonal and reproductive function in patients with bilateral benign germ cell tumors. Several authors recommend ovary-sparing procedures in patients with unilateral appearing lesions (Cass et al. 2001; Pienkowski et al. 2004). However, since many ovarian germ cell tumors have mixed histology, the approach should be cautious. If suspicion for malignancy is low and a pediatric surgeon is expert in minimal invasive surgery, a laparoscopic approach may be considered for benign lesions (Templeman and Fallat 2005; Ehrlich et al. 2007). In general, immature teratomas in children do not respond to chemotherapy (Mann et al. 2008c), so an attempt at complete resection should be undertaken. Figure 39.4.2 shows a large ovarian teratoma in a 2-year-old. A complete resection was accomplished. There have been reports that high-grade immature teratomas in postpubertal women may respond to chemotherapy (Norris et al. 1976). In a pediatric study of teratomas, gliomatosis peritonei was not associated with poor outcome (Göbel et al. 1998d).

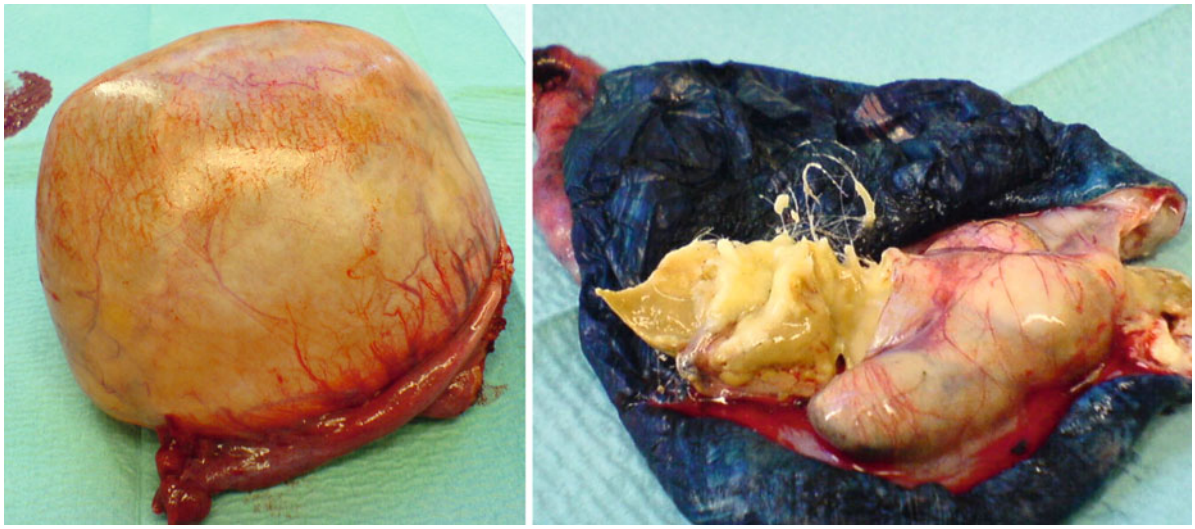

Fig. 39.4.5 Macroscopic presentation of a 2 kg cystic ovarian teratoma prior to and after ink impragnation and opening of the cyst

39.4.6.2 Yolk Sac Tumor and Embryonal Carcinoma of the Ovary

One difficulty in treating ovarian germ cell tumors is that delay in diagnosis often leads to higher-stage disease at presentation. The most common sites of metastases are lymph nodes and lungs. Patients identified as stage I may be managed with surgery and observation. This should be done under the auspices of a clinical trial. In this case overall survival should be the clinical endpoint, rather than event-free survival (tumor events to be specific). What would be an acceptable recurrence rate? In the treatment of many adults with a wide range of cancers, where observation is an option, most patients would choose 50% chance of recurrence, as a determining factor in deciding to receive chemotherapy. Are parents willing to use the same determination for their daughters? If the salvage rate is greater than 95%, observation would make sense. In this way 50% patients would not require toxic chemotherapy Fig. 39.4.6.

The definition of stage I is important. Surgical guidelines are very specific and require careful attention to the other ovary, integrity of the capsule, spillage, and peritoneal washings. However, these strict guidelines for assessing surgical pathologic stage are often violated. This has been documented in a recent pediatric study (Billmire et al. 2004b). Chemotherapy was administered to all stage I and II patients and 100% survived. If chemotherapy is to be omitted, it is an issue. Surgical guidelines as described above should be followed. The strategy of observation with stage I ovarian tumors should be evaluated in clinical trial. Current experience of the MAKEI studies indicates that with a watch-and-wait strategy, progression rate is approximately 20–30%, but overall survival after cisplatin combination chemotherapy is higher than 95%.

If imaging studies show disease beyond the ovary, neoadjuvant chemotherapy must be administered. Subsequent surgery may be required to resect residual disease. This may be important in girls where malignant tumors are often part of a mixed tumor, containing mature or immature teratoma. Surgery is the only treatment for residual mature or immature teratoma. Surgery is often not required for residual gliomatosis peritonei.

Chemotherapy, as previously described in Fig. 39.1.6 from gonadal chapter, should be administered to all patients with stage II–IV ovarian germ cell tumor. A large ovarian yolk sac tumor with retroperitoneal nodal metastases is shown in Fig. 39.4.3. This patient responded to PEB, and a second-look surgery showed no viable tumor.

39.4.6.3 Dysgerminomas

Stage I ovarian dysgerminomas may be treated with surgery alone. Dysgerminomas of the ovary are very sensitive to chemotherapy and radiation therapy.

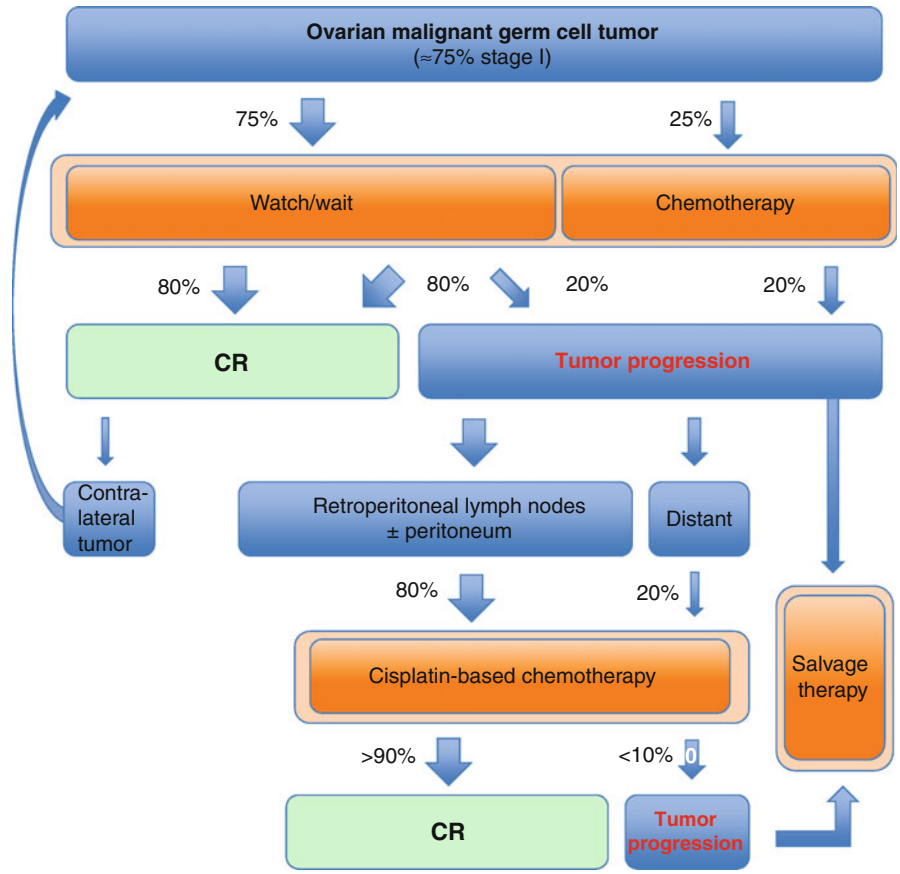

Fig. 39.4.6 Treatment of ovarian malignant germ cell tumors

However, radiation therapy should be avoided due to significant toxicities. It can be used in salvage strategies for recurrence. Chemotherapy regimens have been previously described in Sect. 39.1.1.

39.4.7 Prognosis

Mann et al. reported a 97% 5-year event-free survival rate in girls <15 years of age with mature teratoma and immature teratoma (Mann et al. 2008c). Patients were treated with surgery alone, and no mature or immature teratoma showed any response to chemotherapy. It is recommended that mature teratomas and immature teratomas, in girls less than 15 years of age, be managed without chemotherapy. The management of gliomatosis peritonei is not clear. The German MAKEI study showed no clear association with prognosis (Göbel, Calaminus et al. 2006). The prognosis of ovarian germ cell tumors has improved significantly with the advent of platinum-based chemotherapy. Results, from many international pediatric groups, have been very encouraging (Baranzelli et al. 2000b; Mann et al. 2000d; Göbel et al. 2002b; Cushing et al. 2004d; Rogers et al. 2004d; Schultz et al. 2005). In a US intergroup study, which did not include lymph node sampling or extensive mutilating surgery, greater than 90% EFS was obtained in all stages (stages I–IV). However, if one is to attempt a "watch-and-wait" approach to stage I ovarian germ cell tumors, caution must be observed. In that US trial, adherence to surgical guidelines was poor. Patients survived because they all received chemotherapy (Billmire et al. 2004b).

39.5 Sex Cord Stromal Tumors of the Testis and Ovary

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Giovanni Cecchetto, and Thomas A. Olson

39.5.1 Introduction

Sex cord stromal tumors are a heterogeneous group of rare gonadal tumors. Overall, sex cord stromal tumors represent approximately 10% of all gonadal tumors during childhood. However, the true incidence of sex cord stromal tumors may be underestimated, most likely as a result of incomplete tumor registration. In the Pediatric Tumor Registry of the German Society of Pediatric Oncology and Hematology, sex cord stromal tumors contribute almost 20% to all testicular and ovarian tumors (Schneider et al. 2003b). Accordingly, a continuous rise in the registration rate of ovarian and testicular sex cord stromal tumors has been observed after the development of uniform diagnostic and therapeutic guidelines. Thus, sex cord stromal tumors constitute an illustrative example that with the development of study structures, more patients with rare tumors can be integrated into the clinical and scientific network of pediatric oncology.

Sex cord stromal tumors, in particular, juvenile granulosa cell tumors, constitute characteristic tumors of childhood. Ovarian sex cord stromal tumors may contribute up to one third of all ovarian tumors in early childhood, probably due to the low incidence of germ cell tumors. In the German MAKEI studies (children ≤5 years registered to the MAKEI studies between 1983 and 2000), there were 18 ovarian sex cord stromal tumors compared to 35 ovarian germ cell tumors (Schneider et al. 2003b). Therefore, the clinical management and scientific evaluation of these tumors belong into the hands of pediatric oncologists and not to other subspecialists.

Sex cord stromal tumors develop from the non-germ-cell component of the ovary and may present with a histologic differentiation that in some tumors, may be paradox for the host. Cellular elements, characteristic of the testis, may be seen in ovarian sex cord stromal tumors and vice versa. The rarity of tumors, the heterogeneity, and the difficulty in the correct histopathologic classification of these tumors leave a significant uncertainty with regard to the correct clinical approach to patients with testicular and ovarian sex cord stromal tumors.

39.5.2 Biology

During early embryonic development (fourth week of development), the sex cords arise from the primitive genital ridge or coelomic epithelium. During female gonadal development, the germ cells retain at the periphery of the gonad, enter meiosis, and are surrounded by granulosa cells. The sex cords ultimately develop into ovarian follicles. The development of granulosa cells is dependent on the expression of the winged-helix transcription factor *FOXL2* (Schmidt et al. 2004). In male embryos, sex cords give rise to the rete testis cords that later develop into the seminiferous tubules, thus accompanying the germ cells that further migrate into the gonadal stroma and are surrounded by Sertoli cells. Sertoli cell differentiation and survival depends on the expression of the microRNA processing enzyme *DICER1* (Kim et al. 2010).

Thus, sex cord stromal tumors may develop from sex cord cells or from ovarian stromal cells of the developing gonad. Accordingly, they are histologically heterogeneous and include granulosa cell tumors, Sertoli-Leydig cell tumors, pure Sertoli cell and Leydig cell tumors, as well as theca and granulosa-theca tumors, sclerosing stromal tumors, sex cord stromal tumors with annular tubules, and gynandroblastomas with simultaneous Sertoli and granulosa cell differentiation.

Sex cord stromal tumors may develop in the context of several defined hereditary disorders. Juvenile granulosa cell tumors may be associated with multiple enchondromatosis, syn. Ollier's disease (Clement et al. 1991; Plantaz et al. 1992; Young et al. 1984a). The pathogenetic mechanism has not yet been elucidated to date. In the German series of now more than 150 sex cord stromal tumors, only two patients with Ollier's disease and juvenile granulosa cell tumor have been reported. Adult granulosa cell tumors consistently show mutations of the *FOXL2* gene, a key regulator of granulosa cell development. However, *FOXL2* mutations are only rarely found in juvenile granulosa cell tumors (Shah et al. 2009; Al-Agha et al. 2011). Notably, aberrant *FOXL2* expression may also be observed in some testicular granulosa cell tumors, although no

adult but only juvenile granulosa cell tumors are observed in the testis (Kalfa et al. 2008). Otherwise, no pathognomic genetic aberration has been defined for juvenile granulosa cell tumors, but approximately one third of tumors may show point mutations of stimulatory G proteins (Kalfa et al. 2006). Moreover, the development of juvenile granulosa cell tumors appears to be associated with aberrations in wnt signaling (Boyer et al. 2009).

Genetic analysis of sporadic juvenile ovarian granulosa cell tumors with comparative genomic hybridization has not revealed frequent or characteristic chromosomal imbalances. The majority of tumors show balanced karyotypes. In approx. 25% of patients, chromosomal imbalances, such as gain of the whole chromosome 12, can be found. This analysis has not revealed any correlation between karyotype and clinical outcome (Schneider et al. 2005b). This finding is in line with a previous DNA ploidy analysis of juvenile granulosa cell tumors. In this study, almost half of the tumors showed aneuploid DNA indices. However, no correlation with clinical stage was observed (Jacoby et al. 1992).

Recently, the second most frequent group of ovarian sex cord stromal tumors, the Sertoli-Leydig cell tumors, have been shown to be associated with mutations of the *DICER*1 gene, in particular, in the context of familial multinodular goiter (Rio Frio et al. 2011; Slade et al. 2011). *DICER*1 mutations are associated with pleuropulmonary blastoma (Hill et al. 2009). Of note, a significant proportion of Sertoli-Leydig cell tumor patients suffer from familial multinodular goiter (Whitcomb et al. 1986) or rarely even thyroid cancer (Poiana et al. 2010). In the German series of sex cord stromal tumors, approximately one third of patients with Sertoli-Leydig cell tumors show thyroid disease, and two have developed differentiated thyroid cancer during follow-up of Sertoli-Leydig cell tumor.

There is a pronounced association of Peutz-Jeghers syndrome with sex cord stromal tumors with annular tubules (SCTAT) of both the testis and ovary (Young et al. 1982; Young 2005b; Chang et al. 1998). Approximately one third of SCTAT appear to develop in the context of Peutz-Jeghers syndrome. These tumors usually develop at a younger age than in otherwise healthy patients, and they may develop bilaterally. In contrast, predominantly large cell calcifying Sertoli cell tumors can be found in boys with Peutz-Jeghers syndrome.

39.5.3 Pathology

Testicular and ovarian sex cord stromal tumors present as solid, sometimes lobulated, and partly cystic masses. Tumors are commonly encapsulated, and in the majority of patients, tumors do not grow beyond the gonadal capsule. Thus, testicular sex cord stromal tumors virtually always present as stage I tumors, without local or distant spread. The size of testicular sex cord stromal tumors is low and rarely exceeds 5 cm in diameter. In contrast, ovarian sex cord stromal tumors may present with considerable size. Diameters of more than 20 cm are not uncommon. Some of these large tumors may rupture spontaneously, with tumor spread within the peritoneal cavity. Approximately 5% of ovarian sex cord stromal tumors may develop bilaterally, either as simultaneous or metachronous contralateral tumors. Some tumors may locally infiltrate the Fallopian tube. If tumor spread occurs, it is most commonly observed within the pelvis and the peritoneal cavity and to the locoregional lymph nodes. Hematogenic metastases may develop to the liver, most commonly in relapse situations. In the German MAKEI series of now more than 150 patients, no metastases to lungs, central nervous system, or the skeletal system have been observed.

Since no specific staging system has been developed for sex cord stromal tumors, they are usually staged according to the corresponding germ cell tumors and epithelial cancers (see Sect. 39.1). Testicular tumors are staged either according to the Lugano or COG staging system. Ovarian tumors are staged according to the FIGO or COG staging system.

Histologically, sex cord stromal tumors are categorized according to the predominant cell type of the tumor (Table 39.5.1) (Young 2005a, b). Of note, the histologic differentiation does not follow sex differentiation. Thus, some paradoxical differentiation patterns can be found. Characteristically, sex cord stromal tumors stain positive for inhibin, indicating that these are hormone-producing tumors (Schneider et al. 2003b). Therefore, the immunohistochemical detection of inhibin constitutes a reliable diagnostic marker that distinguishes sex cord stromal tumor from the more frequent germ cell tumors, ovarian carcinoma, or other tumors of different cellular origin (Distelmaier et al. 2006a). Tumors may also stain positive for cytokeratins and vimentin.

Table 39.5.1 Histologic differentiation of testicular and ovarian sex cord stromal tumors and their relative frequencies and characteristic age at presentation

Histology	Testis	Ovary	Age @ presentation
Juvenile granulosa cell tumor (JGCT)	+++	+++	Childhood
Adult granulosa cell tumor (AGCT)	–	++	Adulthood
Sertoli-Leydig cell tumor (SLCT)	–	+++	Adolescence
Sertoli cell tumor	+++	(+)	Childhood/ Adulthood
Large cell calcifying Sertoli cell tumor	+++	–	Childhood
Sclerosing stroma tumor (SCLER)	–	+	Adolescence
Sex cord tumor with annular tubules (SCTAT)	–	+	Adol/ Adulthood
Steroid tumor (STER)	–	+	Adolescence
Thecoma (THEC)	–	++	Adolescence

Granulosa cell tumors constitute the most frequent subtype of sex cord stromal tumors during childhood. In the ovary, adult and juvenile granulosa cell tumors are distinguished by their histologic appearance. Adult granulosa cell tumors only develop within the ovary. These tumors grow slowly, are diagnosed most frequently after the third decade of life, and may develop late recurrences even later than 10 years after diagnosis. In the literature, Call-Exner bodies, formed by a ring of granulosa cells with grooved nuclei and central eosinophilic material, have been often considered the morphologic hallmark of these tumors. Mitotic activity is usually low, and if elevated, has been associated with higher aggressiveness of the tumor. In contrast, juvenile granulosa cell tumors do not display such Call-Exner bodies. They commonly show microfollicular structures with follicle-like structures of variable sizes that are filled with homogeneous eosinophilic material (Young et al. 1984a). Juvenile granulosa cell tumors may show nuclear atypia and high mitotic activity which may sometimes be pronounced. In tumor stage beyond Ia, high mitotic rate (≥20/10 high power fields) correlates with adverse outcome (Schneider et al. 2003a, 2004d). Juvenile granulosa cell tumors of the testis are undistinguishable from their ovarian counterparts.

Sertoli cells constitute the characteristic component of testicular sex cord stromal tumor. Sertoli cell tumors have a peak frequency in the fourth decade of life. However, they may also be diagnosed in childhood. They present with a high variability of well, or poorly tubular, Sertoli cell aggregates. Sertoli cell tumors of childhood are well differentiated and show a favorable outcome. Large cell calcifying Sertoli cell tumors of the testis are characterized by a pronounced fibrosis that may separate the tumor cells into thin cords. Approximately, one fifth of these tumors may develop bilaterally. These tumors are typically associated with Carney's complex (Young 2005b).

Comparable tumors with pure Sertoli cell differentiation are only rarely observed in the ovary. Here, Sertoli cell differentiation is characteristically seen only within Sertoli-Leydig cell tumors (SLCT), which include both cellular components (Young and Scully 1985). Of note, this tumor type is not observed within the testis. SLCTs may show a highly variable grade of differentiation. In highly differentiated SLCTs, tubular structures with Sertoli cells predominate and are accompanied by sheets of Leydig cells. As a result of hormone production, the ovarian stroma may show luteinization. Tubular structures are lost with lower grade of differentiation. Retiform and microtubular differentiation may be described, and by some authors, are considered distinct histopathologic patterns (Young et al. 1984b). In some tumors, heterologous differentiation, e.g., with intestinal epithelium, may develop. These histologic features, low differentiation, retiform pattern, and heterologous differentiation, have all been associated with adverse outcome (Young and Scully 1985).

Other very rare sex cord stromal tumors include sex cord stromal tumors with annular tubules, sclerosing stroma tumors, thecomas, and steroid cell tumors. Considering the heterogeneity of these tumors and the difficulties in distinguishing them from germ cell tumors or small cell ovarian carcinomas, a reference pathologic evaluation at an experienced paidopathologic or gynecopathologic center is strongly recommended.

Characteristic histologic samples of JGCT and SLCT are demonstrated in Figs. 39.5.1–39.5.3.

39.5.3.1 Clinical Presentation

Testicular sex cord stromal tumors typically present as an indolent scrotal mass. Since juvenile granulosa cell tumors often develop within the first months of life,

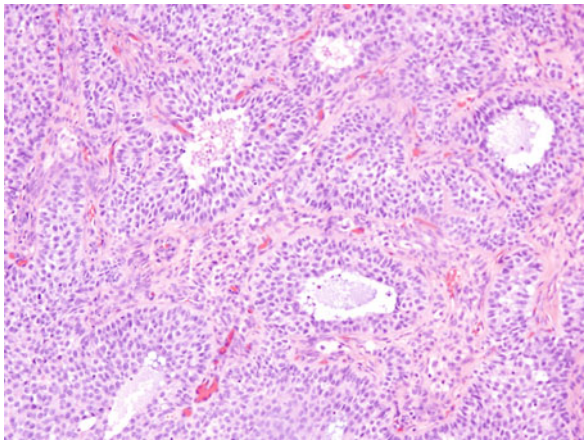

Fig. 39.5.1 Histologic samples from juvenile granulosa cell tumors (H+E)

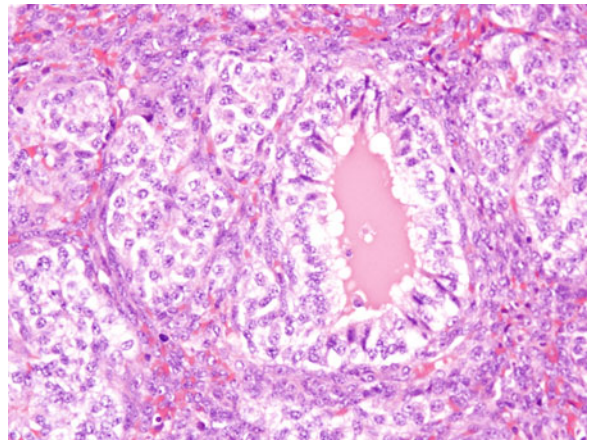

Fig. 39.5.3 Histologic samples from juvenile granulosa cell tumors (H+E)

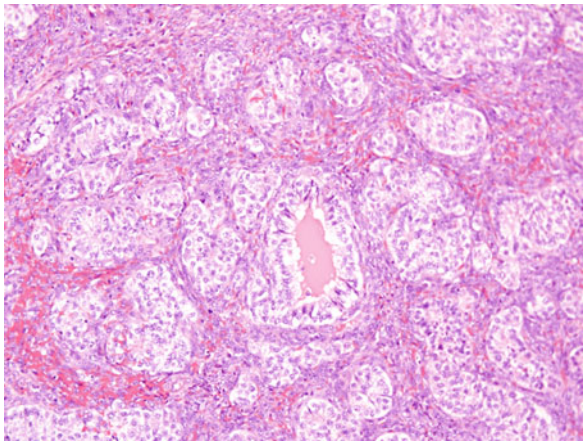

Fig. 39.5.2 Histologic samples from juvenile granulosa cell tumors (H+E)

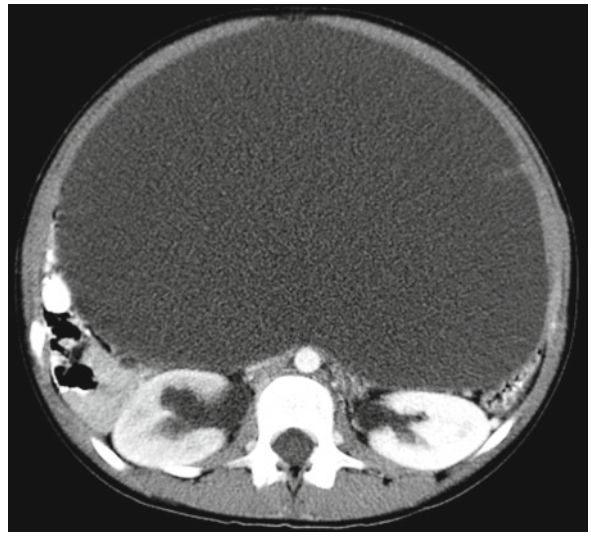

Fig. 39.5.4 CT scan of a large cystic juvenile granulosa cell tumor

these tumors may be present at birth. In contrast, only one in four ovarian sex cord stromal tumors are apparent as a large indolent mass (Fig. 39.5.4). Almost half of the patients have abdominal pain. Approximately 10% of patients present with an acute abdomen, caused either by spontaneous tumor rupture or ovarian torsion. Two thirds of ovarian sex cord stromal tumors were associated with clinical symptoms related to production of sex hormones by the tumor (Schneider et al. 2003a). Characteristically, infants and children may present with signs of isosexual precocity, including breast enlargement, pubarche, and vaginal bleeding. In postpubertal girls, tumors may lead to primary or secondary amenorrhea and unspecific signs of virilization such as pronounced acne. These are characteristic signs of Sertoli-Leydig cell tumors (Schneider et al. 2003a).

As other steroid hormone–producing cells, OSCST also produce inhibin. Free inhibin can be measured in the serum and may serve as a serological tumor marker during follow-up. However, the diagnostic value may sometimes be hampered by the physiologically broad normal range in healthy prepubertal children (Crofton et al. 2002a, b).

In some rare patients, SLCT may produce AFP, which can be detected serologically. Histologically, most of these tumors resemble SLCT with retiform, often hepatoid, differentiation and heterologous elements (Young et al. 1984b).

39.5.4 Diagnostic Assessment and Differential Diagnosis

Due to the rarity of sex cord stromal tumors, in most patients the diagnosis of sex cord stromal tumor will not be established until histologic confirmation. Nevertheless, in particular, in young children, with tumor marker (AFP, βHCG) negative gonadal tumors, sex cord stromal tumors should be considered. The diagnostic and radiographic assessment is almost identical to that of gonadal germ cell tumors (Table 39.5.2). Since these tumors do not metastasize beyond the abdomen, whole-body staging is not required.

OSCST have to be distinguished from ovarian germ cell tumors, epithelial ovarian cancer, including small cell carcinoma of the hypercalcemic type, and gonadal tumors of different histogenesis, such as leukemia/lymphoma or sarcoma. Tumors presenting with vaginal bleeding in infants must be discriminated from the rare vaginal yolk sac tumors. Clinically, the evaluation of serologic tumor markers alpha-fetoprotein (AFP) and β-human chorionic gonadotropin helps in the differential diagnosis of secreting malignant germ cell tumors. Therefore, it is mandatory to measure these tumor markers preoperatively (Schneider et al. 2001h).

In some rare patients, the distinction of juvenile granulosa cell tumors from small cell ovarian carcinoma of the hypercalcemic type may be particularly difficult, since the latter may mimic the pseudofollicular growth pattern characteristic of JGCTs (Distelmaier et al. 2006b). In these situations, the immunohistochemical detection of inhibin constitutes an important diagnostic hallmark of ovarian sex cord stromal tumors. Inhibin positivity has not been observed in small cell ovarian carcinoma, while virtually all sex cord stroma tumors stain positive (Schneider et al. 2003b).

Lastly, mutation testing for DICER1 may be performed in Sertoli-Leydig cell tumors within clinical studies. The clinical and prognostic impact is not yet evaluated prospectively, but positive findings may

Table 39.5.2 Specific diagnostic strategy in testicular or ovarian sex cord stromal tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Gynecological and pubertal history? Vaginal bleeding, breast development, etc.? Thyroid disease? Inherited syndromes (Mb. Ollier's, Peutz-Jeghers, etc.)?
Phys. examination	Pubertal status, goiter, abdominal pain
Laboratory assessment	
AFP, β-HCG	Malignant germ cell tumor with yolk sac tumor (consider age-related reference values) or choriocarcinoma.
	Note: Some Sertoli-Leydig cell tumors may show AFP levels up to 1000 μg/L
Inhibin	Serological marker of hormone-secreting sex cord stromal tumors
Estrogen, DHEAS, LH, FSH	Endocrinological assessment
Clinical chemistry incl. calcium	Calcium may be elevated in ovarian small cell carcinoma (but also in rare germ cell or sex cord stromal tumors)
Creatinine clearance/ cystatin c	Assessment of renal function (in case of chemotherapy)
Radiographic assessment	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/ spermatic cord, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/ spermatic cord, lymph node or liver metastases
Chest X-ray	Lung metastases (extremely unlikely)
Note: Metastases beyond the abdomen are exceedingly rare. Therefore, extended radiographic assessment is required in case of clinical symptoms only	
Histologic assessment	
H&E	Classification and grading according to WHO
Mitotic rate per 10 HPF	Prognostic assessment (in particular, juvenile granulose cell tumors)
Inhibin	Positive for sex cord stromal tumors
AFP	Yolk sac tumor, may also be positive in retiform Sertoli-Leydig cell tumors

indicate association with thyroid disease or metachronous tumors (Rio Frio et al. 2011; Slade et al. 2011).

39.5.5 Treatment and Prognostic Markers – Review of the Literature

The current literature includes only a few and mostly retrospective series of patients with testicular sex cord stromal tumors. Most publications focus on adult patients with sex cord stromal tumors or represent case reports and small patient cohorts, collected at single centers. This may be explained by the lack of cooperative study structures for sex cord stromal tumors, as have successfully been established for germ cell tumors. Thus, many patients have been registered on either the corresponding national germ cell tumor trial or the national rare tumor study group.

The largest series of ovarian sex cord stromal tumors has been reported by the German MAKEI study group (Schneider et al. 2003a, b). This series has verily focused on the pathologic differential diagnosis and prognostic factors (Schneider et al. 2003b) and the prognostic impact of staging (Schneider et al. 2003a, 2004d). In this and other studies, the favorable outcome of completely resected stage I ovarian sex cord stromal tumors has been demonstrated (Cecchetto et al. 2011; Kalfa et al. 2005). In stage Ic or higher (i.e., microscopic tumor spread), prognosis was inferior if tumors ruptured spontaneously or showed malignant ascites compared to those with only intraoperative tumor violation, e.g., during laparoscopic surgery (Schneider et al. 2004d). In stage Ic or higher, pronounced mitotic activity (>20 mitoses per 10 high power fields) was also associated with adverse outcome. In stages II–III, the impact of cisplatin-based chemotherapy in accordance to current germ cell tumor protocols has been demonstrated (Schneider et al. 2002c; Cecchetto et al. 2011).

This experience is further supported by case reports that argue for adjuvant chemotherapy in advanced stage JGCT. Colombo reported on a girl with a stage III JGCT that achieved complete remission for at least 7 months after PVB chemotherapy (Colombo et al. 1986). Powell reported on a 13-year-old primigravida with a stage IIIb JGCT that was successfully treated with a combination of methotrexate, actinomycin, and chlorambucil. The patient has remained in complete remission for 7 years, during which time, she gave birth to further children. The same authors reported on two stage III tumors successfully treated with surgical debulking and carboplatin and etoposide. In addition, a patient with recurrent JGCT with liver metastases achieved complete remission for 44 months after surgery and six cycles of bleomycin and Taxol (Powell and Otis 1997; Powell et al. 1993, 2001).

The largest published series, focusing specifically on ovarian juvenile granulosa cell tumors, analyzed 125 adolescent and adult patients, with follow-up data in 83 patients (Young et al. 1984a). In this series, there were only 2/80 stage I tumors, but all three stage II tumors were fatal. Additional clinical and histologic parameters did not contribute to the prognostic assessment. The largest series of Sertoli-Leydig cell tumors has been reported by the same study group and included 207 patients. Follow-up information was available in 164 patients (Young and Scully 1985). Outcome correlated with both stage and histologic differentiation, and both parameters closely correlated with each other. All well-differentiated SLCT behaved clinically benign, whereas 11% of SLCT with intermediate differentiation and 59% of poorly differentiated SLCT (all stages II-III) showed a malignant course. In particular, those tumors with retiform differentiation and/or heterologous elements were unfavorable.

Two significant studies by the French Pediatric Oncology Group each report on 40 ovarian juvenile granulosa cell tumors treated between 1965 and 1990, and 1990 and 2004, respectively (Kalfa et al. 2005; Plantaz et al. 1992). The authors report that young (prepubertal) age appears to correlate with more favorable diagnosis, in particular, if early diagnosis is established based on assessment of isosexual precocity. However, delayed diagnosis is associated with a higher risk of tumor ruptures and higher tumor stage. Thus, manifestation with acute abdominal pain correlated with adverse outcome, both in prepubertal children and in postpubertal adolescents.

Data on pediatric Sertoli-Leydig cell tumors in children and adolescents are even more limited. Recently an international cooperative analysis of eXpert has been performed, which included 42 patients from Poland, Italy, France, and Germany. In this analysis, event-free survival was 0.66 and overall survival 0.83, which is inferior to that observed in juvenile granulosa cell tumors. Again, outcome was excellent in completely resected (stage Ia) tumors. Only two metachronous contralateral tumors have been reported in this

Table 39.5.3 Proposed therapeutic algorithm in testicular and ovarian sex cord stromal tumors

Site	Stage	Histology	Neoadjuvant chemotherapy	Surgical therapy	Adjuvant chemotherapy
Testis	I	All	–	Inguinal orchiectomy	Watch & wait
	>I	All	–	Inguinal orchiectomy	≥4×PEI/BEP
Ovary	Ia	All	–	Ovariectomy	Watch & wait
	Ic	Sertoli-Leydig	–		4×PEI/BEP
	Ic, intraop.	Juv. granulosa, others	–		Watch & wait
	Ic, preop.		–		4×PEI/BEP
	II–III	All	PEI/BEP	Adenectomy	>4×PEI/BEP[a]

[a]A total of 5–6 cycles of chemotherapy including preoperative chemotherapy is recommended

group. In contrast, almost half of patients with microscopic spread (e.g., malignant ascites, preoperative rupture) or even only intraoperative tumor rupture relapsed. Metastases are rare and are only found at diagnosis in approximately 10% of patients. Metastatic disease can successfully be managed with cisplatin-based chemotherapy (e.g., PEI).

Current literature indicates that the prognosis of testicular sex cord stromal tumors is excellent (Cecchetto et al. 2011; Harms and Kock 1997). Virtually, no patients develop metastases. If they do, these tumors show poorly differentiated histology and require aggressive therapy, comparable to that for metastatic germ cell tumors (Ross et al. 2002). Thus, if a metastatic testicular sex cord stromal tumor is diagnosed, the histopathologic diagnosis should first be questioned and be specified by reference evaluation. In the German series and in all currently published pediatric series, only very rare recurrences or fatal outcomes have been reported.

39.5.6 Proposed Therapeutic Strategy

It should be considered that the following recommendation is not based on prospective randomized trials but represents the experience gained in comparably small prospective series of patients. Basically, the following strategy is based on the concept of the MAKEI study, which has also been adopted as a consensus and guidance for the COG rare tumor group (Table 39.5.3). The therapeutic algorithm separates patients by tumor site, stage, and histologic parameters. The uniform treatment stratification, the incorporation of uniform central pathology review, and the central evaluation and documentation of clinical data may hopefully facilitate validation and further optimization of therapy of these rare tumors.

39.5.6.1 Testicular Sex Cord Stromal Tumors

Since virtually all tumors present as localized stage I tumors, resection will constitute the only therapy of these tumors. In principle, orchiectomy after high inguinal incision and ligation of the spermatic cord constitutes the gold standard. Considering the overall favorable diagnosis, there has been some debate as to whether tumor excision after scrotal excision and even organ sparing surgery (e.g., enucleation of the tumor) may also be appropriate. However, it should be noted that this strategy has not been validated prospectively. Moreover, it remains questionable whether organ-sparing surgery may indeed contribute to further reproductive function and quality of life (Tröbs et al. 2007). The extremely rare metastatic tumor should be treated according to the corresponding concept for ovarian sex cord stromal tumors.

39.5.6.2 Ovarian Sex Cord Stromal Tumors

In all patients, the tumor resection (tumor ovariectomy/tumor adnectomy) constitutes both a diagnostic and therapeutic procedure. The surgical resection should follow the same principles as that for malignant germ cell tumors. The MAKEI data do not indicate that radical retroperitoneal lymph node resection or extended lymph node sampling is required in all ovarian sex cord stromal tumors, because lymph node metastases have been observed only rarely and most commonly in (extended) relapse situations. However, if lymph node metastases are detected (e.g., in relapse situations), all visible metastases should be resected. Ideally, this should be done after preoperative chemotherapy. The German, French, and Italian data presented above suggest that no adjuvant therapy is necessary in stage Ia tumors.

The data reported by the German MAKEI study group represents the first cohort of patients prospectively registered and treated according to a uniform

strategy. Based on these data, a risk stratification for adjuvant chemotherapy can be proposed for patients with stage Ic, II, or III tumors:

39.5.6.3 Stage Ic

In stage Ic, the decision to add adjuvant chemotherapy is most difficult. Tumors in which a microscopic tumor spread is suspected or proven (but no pathologic evidence of peritoneal metastases) are classified as stage Ic. According to FIGO, tumors may be classified as stage Ic for several reasons: A preoperative tumor rupture may have occurred, and in others the cytological analysis of peritoneal washings or ascites provides evidence of malignant tumor cells. In contrast, a tumor may also be classified stage Ic if the tumor has been punctured or the capsule has otherwise been violated in situ. In this case the tumor capsule must be intact prior to surgery (intraoperative violation of tumor capsule).

The previous analysis of a cohort of patients, which predominantly included juvenile granulosa cell tumors, has demonstrated that intraoperative violation of the tumor capsule does not increase risk of recurrence. In contrast, a high relapse rate (comparable to stages II–III) has been observed in those patients whose tumor has been ruptured prior to surgery or if the ascites contains malignant cells.

This observation indicates that thorough documentation and critical evaluation of the clinical and surgical report are mandatory. Cytological analysis of ascites/peritoneal washings is indispensable. In cases with incomplete documentation or missing cytological evaluation, the assessment of the proliferative activity of the tumors may help with regard to risk assessment, but nevertheless a higher grade of uncertainty remains. In the current experience of the MAKEI study, the application of four cycles of cisplatin-based chemotherapy is sufficient to control microscopic tumor spread. In Germany, PEI (see Sect. 39.1, Table 39.1.4) is recommended. In other countries, PEB is applied according to the respective national germ cell tumor protocol. There are no data supporting which regimen is more effective. Data on carboplatin are limited.

As mentioned above, this experience is based on the analysis of cohorts that predominantly included juvenile granulosa cell tumors. The most current analysis, specifically focusing on Sertoli-Leydig cell tumors, has demonstrated that these may develop recurrences even after only minute intraoperative tumor violation (Schneider et al. 2010). Most of these recurrent tumors show additional prognostically unfavorable features such as low histologic differentiation, retiform pattern, or heterologous elements. Thus, the decision in favor of or against chemotherapy remains individual; however, the approach for these tumors obviously has to be more aggressive than that for juvenile granulosa cell tumors.

39.5.6.4 Stages II–III

In stages II–III, micro- or macroscopic spread with peritoneal or lymph node metastases has occurred. It is very obvious that surgical treatment alone will not be curative but must be supplemented with adjuvant chemotherapy. In the past, cure of ovarian sex cord stromal tumors has been reported in single cases only (Kudelka et al. 1998, Powell and Otis 1997; Powell et al. 1993, 2001). The MAKEI study group was the first to report a series of patients with advanced tumor stage, who were treated with adjuvant cisplatin-based combination chemotherapy (Calaminus et al. 1997b; Wessalowski et al. 1995; Schneider et al. 2002c). In these series on advanced juvenile granulosa cell tumors, high proliferative activity distinguishes patients with poor prognosis. In addition to proliferative index, age also appears prognostic (Schneider et al. 2003a).

There are several issues that remain to be addressed critically. The indication for chemotherapy and the minimum amount of chemotherapy necessary in stage Ic tumors are ill-defined. The German data suggest that among stage Ic patients, a subgroup of patients at high risk can be identified through histologic assessment. These patients may be suitable for adjuvant chemotherapy. However, the limited data available from our analysis does not allow definition of the required chemotherapy for tumors at stage Ic or higher. In the Germany study, all patients with stage II to III tumors received at least four cycles. Considering other studies with less favorable outcome, we would not advocate less but rather argue for extension to six cycles. Although to a certain extent, chemotherapeutic regimens varied with the consecutive MAKEI protocols. All but one patient received chemotherapy that included cisplatin and etoposide, mostly as part of three-agent regimens. Therefore, it appears meaningful to include these two drugs into a three-agent combination regimen such as cisplatin, etoposide, and ifosfamide (PEI).

Lastly, alternative strategies must be developed for refractory tumors. In our experience, regional deep hyperthermia has resulted in complete remissions in recurrent or refractory OSCST, although experience

with this approach is limited and responses did not translate into durable remissions longer than 2 years (Wessalowski et al. 1995).

39.5.7 A Call for International Collaboration

Sex cord stromal tumors are currently registered to germ cell tumor trials or rare tumor registries in a minority of countries. However, these tumors constitute a potentially deadly threat. It is mandatory to develop international networks for counseling, scientific evaluation, and validation of therapeutic concepts. The authors have been continuously contacted for consultation on a significant numbers of patients. However, if the data of these patients are not collected centrally and if the involved requesting partner does not provide follow-up data, this valuable clinical information will be lost to the scientific community. Future patients will not benefit from the experience gained in other patients in comparable, rare situations.

39.6 Ovarian Adenomas, Ovarian Carcinoma, and Ovarian Small Cell Carcinoma

Dominik T. Schneider and Thomas A. Olson

39.6.1 Introduction

In addition to the more common ovarian germ cell tumors and sex cord stromal tumors, there are several less frequent and poorly studied pediatric epithelial ovarian tumors. Their clinical spectrum varies from benign adenomas and borderline tumors to adenocarcinoma and highly aggressive tumors, such as ovarian small cell carcinoma of the hypercalcemic type (OSCCHT). The latter was first defined, as a distinct entity, 30 years ago (Dickersin et al. 1982). It may be the most aggressive ovarian tumor during childhood and adolescence. Until recently, OCCCHT has been considered almost inevitably fatal.

All these tumors usually fail to be identified in tumor registries. A remarkable gap between true incidence and registration exists. An epidemiological analysis of the North American Association of Cancer Registries revealed that in children younger than 15 years, ovarian carcinomas are three times more common than sex cord stromal tumors. In adolescents from 15 to 19 years of age, they were almost as common as germ cell tumors (Young et al. 2003). These epidemiologic data stand in stark contrast to the little experience reported in the literature. To a certain degree, this discrepancy can be attributed to the circumstance that epithelial ovarian tumors are not routinely registered on prospective studies of gonadal tumors, where the main focus is germ cell tumors. Even in a large pediatric oncologic ovarian tumor registry, the German MAKEI registry, an average of two to three epithelial or carcinomatous ovarian tumors is reported per year. This compares to more than ten sex cord stromal tumors. Other international pediatric study group, that register ovarian tumors experience comparably low registration rates, too. There is an obvious trend. These children and adolescents are seen, treated, and followed up by gynecologists. As a result, they are not evaluated by pediatric oncologists. Nevertheless, pediatric oncologists are often consulted, in particular, when these patients present with advanced

Table 39.6.1 Diagnostic assessment in ovarian epithelial tumors and ovarian small cell carcinoma, hypercalcemic type

Procedure	Specific questions
Clinical assessment:	
Medical history	Gynecological and pubertal history? Vaginal bleeding, breast development etc.? Familial cancer (ovary, breast)?
Phys. examination	Pubertal status, abdominal pain
Laboratory assessment:	
– AFP, ß-HCG	Malignant germ cell tumor with yolk sac tumor (consider age-related reference values) or choriocarcinoma; *Note:* Some Sertoli-Leydig cell tumors may show AFP levels up to 1000 µg/L
– Inhibin	Serological marker of hormone secreting sex cord stromal tumors
– Estrogen, DHEAS, LH, FSH	Endocrinological assessment
– Clinical chemistry incl. calcium	Calcium may be elevated in ovarian small cell carcinoma (but also in rare germ cell or sex cord stromal tumors)
– Creatinine clearance/ cystatin c	Assessment of renal function (in case of chemotherapy, renal impairment may occur as a complication of hypercalcemia)
Radiographic assessment:	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/spermatic cord, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/spermatic cord, lymph node or liver metastases
Chest X-ray	Lung metastases (extremely unlikely)
Note: OSCCHT may show metastases beyond the abdomen. Therefore, extended radiographic assessment is required in case of clinical symptoms.	
Histologic assessment:	
H&E	Classification and grading according to WHO
Vimentin, cytokeratin	Double positive in OSCCHT
Inhibin	Positive for sex cord stromal tumors, negative in ov. carcinomas
AFP, β-HCG	Exclusion of secreting germ cell tumors

or recurrent disease. It is clearly important to early identify those patients that are at the highest risk to develop fatal disease. The best example might be OSCCHT, since these patients have to be treated intensively at any stage of disease.

39.6.2 Clinical Presentation and Diagnostic Assessment

Ovarian cystadenomas, borderline tumors, and most ovarian carcinomas present with local symptoms such as local swelling, obstipation, dysuria, or abdominal pain. Ovarian torsion or spontaneous rupture may mimic acute abdomen, necessitating emergency procedures. Paraneoplastic symptoms are rarely observed. Approximately, two thirds of OSCCHT may present with significant hypercalcemia, sometimes leading to renal failure. However, other ovarian neoplasms, such as dysgerminoma, may also be associated with hypercalcemia, though less frequently (Young et al. 1994) Table 39.6.1.

On histopathologic examination, most epithelial tumors present as cystic adenomas (cystadenomas) or borderline tumors. True classical ovarian carcinomas may be diagnosed, too. The majority of these tumors present at a low local stage. In contrast, OSCCHT may present with extensive intra-abdominal metastases. Two thirds of patients with OSCCHT may exhibit a paraneoplastic hypercalcemia. OSCCHT is predominantly a unilateral tumor that most commonly affects young women in the second and third decade of life. Less than 30% of tumors develop in patients younger than 20 years of age and less than 1% in children. The

youngest patient, reported to date, has been 14 months (Florell et al. 1999; Young et al. 1994).

The diagnostic work-up is comparable to ovarian germ cell tumors and sex cord stromal tumors (see Sect. 39.1.4, Table 39.4.2; Sect. 39.1.5, Table 39.5.1).

Tumor markers AFP and β-HCG serve to help exclude the diagnosis of malignant nondysgerminomatous germ cell tumors. Inhibin, androgens, and estrogens are within the normal range in epithelial tumors. CA125 is the characteristic tumor marker and can be utilized for follow-up monitoring. However, CA125 elevation may also be observed in germ cell tumors and sex cord stromal tumors (personal observation) or in benign conditions such as pregnancy, endometriosis, or Crohn's disease (Robertson et al. 2002).

Radiographic assessment includes abdominal ultrasound, supplemented with magnetic resonance tomography. The pattern of lymph node metastases may vary by site. Left ovarian tumors primarily metastasize to lymph nodes in the renal hilum, whereas right ovarian tumors metastasize to paracaval lymph nodes. A chest X-ray is indicated to exclude rare lung metastases. In OSCCHT, a brain MRI and bone scan should be performed if patients show clinical signs of skeletal or neurological involvement.

In case of classical ovarian carcinoma, the family history should specifically focus on a history of breast cancer. Genetic counseling and testing for BRCA gene mutations should be considered. However, one should be aware that OSCCHT might also occur in families without evidence of BRCA mutations (Distelmaier et al. 2006b) (Lamovec et al. 1995; Longy et al. 1996). In the German pediatric series, two pairs of siblings have been observed among a total of currently 15 patients.

The differential diagnosis of pelvic masses includes benign ovarian cysts, other ovarian tumors, and benign or malignant masses that develop from the bowel, urinary tract, or other pelvic structures. The most difficult diagnosis of cystadenomas may be benign ovarian cysts. Ovarian cysts are often asymptomatic and are detected accidentally during ultrasound. In a large series including more than 1,800 prepubertal patients, ovarian cysts were detected in 5% of patients (Millar et al. 1993). However, benign cysts rarely exceed 5 cm in diameter and often show spontaneous regression during follow-up. In contrast, ovarian tumors are most commonly diagnosed with a diameter of greater than 10. The spectrum of differential diagnoses of ovarian cysts in postpubertal adolescents is broader and includes pregnancy, tubal lesions, and genital obstruction, such as imperforate hymen.

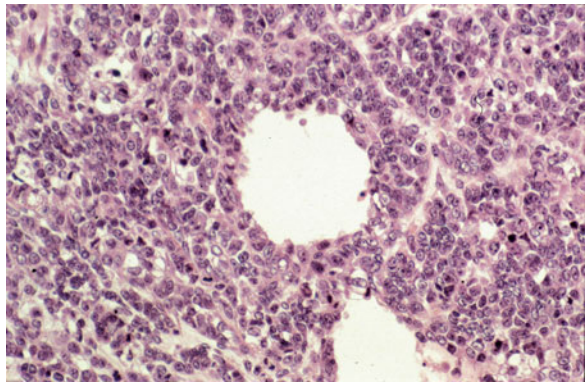

Fig. 39.6.1 Ovarian small cell carcinoma of the hypercalcemic type in a 16- year old girl (H&E, 400×). Histologically, the tumor is characterized by sheets of closely packed, small cells with scanty cytoplasm forming scattered follicle-like structures, and the morphologic similarity to sex cord stromal and germ cell tumors may pose significant problems in establishing the correct diagnosis

Pathologic examination follows the same principles as for ovarian germ cell and sex cord stromal tumors. It should be noted that the majority of OSCCHTs are first misdiagnosed (Distelmaier et al. 2006b). Therefore, consultation with a reference pathologist should be considered for all ovarian tumors, ideally prior to the start of chemotherapy.

On histopathologic examination, OSCCHTs show a solid growth pattern with admixed pseudofollicular structures and occasional areas of necrosis and hemorrhage (Fig. 39.6.1). The mitotic rate is usually high with an average of 23 mitoses of 10 high power fields (range 17–29/10 HPF) in the German series. Some tumors are classified as a large cell variant. Others may show a pronounced hemangiopericytic growth pattern or pronounced rhabdoid features. The most important and difficult histopathologic differential diagnosis is juvenile granulosa cell tumor, which in contrast to OSCCHT, shows inhibin positivity (Schneider et al. 2003c). All OSCCHT centrally examined at the German Childhood Tumor Registry stained negative for inhibin, alpha-fetoprotein, human placental like alkaline phosphatase, and beta-human chorionic gonadotropin upon immunohistochemical examination. Characteristically, the tumors show co-expression of cytokeratins and vimentin.

Tumors are staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (Benedet et al. 2000) (see Sect. 39.1.4, Table 39.4.3).

39.6.3 Therapy

In cystadenomas, borderline tumors, and carcinomas, complete tumor resection constitutes the cornerstone of treatment. In most gynecology-oncology centers, tumor resection is done laparoscopically. However, this technique has not been validated in children and adolescents with ovarian tumors. No prospective studies have compared conservative and laparoscopic approaches in children and adolescents. The tumor-bearing ovary is removed in most patients. Again, organ-sparing surgery is not validated in children and adolescents. However, in bilateral tumors, it remains the only (but still experimental) approach to conserve fertility. During surgery, it must be decided whether the fallopian tube has to be removed, too. Since most tumors are limited to the ovary, routine adenectomy and hysterectomy are not justified. Given the perspective of chemosensitive tumors, hysterectomy is obsolete in children and adolescents.

Normalization of renal function must be the first therapeutic intervention when OSCCHT presents with hypercalcemia. This can be achieved with aggressive hydration and diuretic therapy with furosemide. In OSCCHT, complete resection is a prerequisite for cure. However, resection alone is often not sufficient for definite cure: In the German series, all four stage I patients, followed according to a watch-and-wait strategy, relapsed (Distelmaier et al. 2006b). In the report by Young, less than 10% of adolescent stage I patients survived (Young et al. 1994). Nevertheless, mutilating surgery, such as hysterectomy, should be avoided, even in OSCCHT with pelvic and peritoneal metastases, as recent data indicate that these tumors are chemosensitive. Thus, in a multimodal therapy, the aim is cure with preservation of a chance of fertility.

Ovarian cystadenomas and borderline tumors usually present as stage I tumors and require no additional adjuvant therapy. Metastatic ovarian carcinomas are most commonly treated with a combination of carboplatin and Taxol, in accordance to current gyne-oncology protocols. The pediatric experience in these tumors is limited. During the last decade, nine cystadenomas and borderline tumors as well as two ovarian carcinomas have been reported to the German study group. All were stage one and have been observed without adjuvant treatment. No relapses were reported (unpublished information).

39.6.4 Review on Multimodal Therapy of OSCHHT in Adults and Children

The prognosis of OSCCHT is generally believed to be poor and almost inevitably fatal. In the largest series reported to date, event-free survival was 33% in stage Ia, 10% in stage Ic, and 6.5% in stages II–IV. Notably, half the registered patients showed abdominal or peritoneal tumor spread, corresponding to FIGO stages II–III. In addition, young age was associated with a particularly poor prognosis, even in low-stage tumors. Less than 10% of children and adolescents with stage IA OSCCHT survived (Young et al. 1994).

The ideal multimodal treatment for OSCCHT has not yet been defined. However, it is apparent from the above-mentioned data that treatment of this tumor type requires a multimodal aggressive approach.

Senekjian et al. first reported on five patients with ovarian small cell carcinomas treated with a combination of vinorelbine, cisplatin, cyclophosphamide, bleomycin, Adriamycin, and etoposide (Senekjian et al. 1989). Despite initial promising responses to chemotherapy, four of five patients died of disease.

In the largest series on OSCCHT, Young et al. mention that the most patients received some form of adjuvant chemotherapy (Young et al. 1994). However, detailed information on only seven patients with favorable response to therapy, either during first- or second-line therapy, is provided. As outlined in Table 39.6.2, patients received combination chemotherapy with various regimens that included anthracyclins, etoposide, cisplatin, and alkylating agents. Three patients had radiation therapy. One of the seven patients is in first complete remission (CR).Three are in second CR. One is alive with disease and two are dead (Table 39.6.2) (Young et al. 1994). However, this report includes no information regarding the single and cumulative doses of either radio- or chemotherapy. Therefore, no specific conclusions can be drawn other than that some selected patients may benefit from adjuvant therapy.

Table 39.6.2 Summary of therapeutic regimen administered in series using coventional chemotherapy ± radiotherapy but without high dose chemotherapy (this table includes only drugs included in the first-line chemotherapy)

Study	No	Stage	Irradiation	Taxol	Platin derivates	VP-16	Alkylat. Agents	Anthra-cyclins	Best status	Outcome	Follow-up (months)
Young[a]	1	Ia	+	–	+	–	–	–	CR	CR-2	45
	2	Ia	–	–	+	–	–	–	CR	CR-2	53
	3	Ia	–	–	+	+	–	+	CR	DOD	81
	4	IIb	+	–	+	+	+	+	CR	CR-2	84
	5	III	+	–	–	–	–	–	CR	DOD	66
	6	III	–	–	+	+	+	+	CR	AWD	24
	7	III	–	–	+	+	–	+	CR	NED	30
Harrison	1	I	–	–	+	+	–	–	CR	NED	10
	2	Ia	45 Gy	–	+	+	–	–	CR	NED	60
	3	Ic	45 Gy	–	+	+	–	–	CR	NED	51
	4	Ic	–	–	+	–	+	+	CR	DOD	29
	5	Ic	–	+	+	+	–	–	CR	CR-2	16
	6	Ic	45 Gy	–	+	+	–	–	CR	NED	71
	7	Ic	40 Gy	+	+	+	–	–	CR	NED	59
	8	Ic	45 Gy	–	+	+	–	–	CR	NED	65
	9	Ic	50 Gy	+	+	+	–	–	PR	AWD	8
	10	Ic	–	+	+	–	–	–	CR	AWD	16
	11	III	–	+	+	+	–	–	SD	DOD	6
	12	IIIc	–	+	+	-	–	–	CR	DOD	11
	13	IIIc	50 Gy	–	+	+	–	–	CR	NED	5
	14	IIIb	–	–	+	+	–	–	CR	DOD	7
	15	IIIb	–	+	+	–	–	–	PD	DOD	3
	16	IIIc	–	–	+	–	–	–	CR	DOD	13
	17	n.d.	–	+	+	–	–	–	PD	DOD	2
Senekijan	1	Ia	–	–	+	+	+	+	CR	NED	29
	2	Ia	–	–	+	+	+	+	CR	DOD	18
	3	IIc	45 Gy	–	+	+	+	+	CR	DOD	11
	4	IIIa	45 Gy	–	+	+	+	+	PR	DOD	13
	5	IIIa	–	–	+	+	+	+	CR	DOD	15

[a]Only the patients with "favourable response" to therapy

Additional detailed and more encouraging information can be retrieved from the more recent report by Harrison et al. which included 17 adult patients treated in Australia, Canada, and Europe between 1989 and 2004 (Table 39.6.2) (Harrison et al. 2006). Ten patients had stage I tumors, six with stage III, and one patient with an unknown tumor stage. Surgical resection included oophorectomy (six patients), unilateral adenectomy (three patients), or hysterectomy with (bilateral) adenectomy (seven patients). After surgery and prior to the start of adjuvant chemotherapy, three patients had tumor residues larger than 1 cm. In accordance with recommendation discussed above, all patients received adjuvant chemotherapy regardless of initial tumor stage. The main drugs are listed in Table 39.6.2. Briefly, cisplatin-based regimens, in combination with etoposide according to strategies applied in malignant germ cell tumors, were administered. Notably, Taxol-based regimens, which are commonly used in other types of ovarian carcinoma, did not prove successful. Only one of eight patients treated with Taxol remains in continuous remission. This finding is in line with the observation, from the German series, that Taxol demonstrates only limited efficacy both in first-line and salvage therapy. The authors conclude that radiotherapy has a significant therapeutic impact. In their experience, the outcome of stage I tumors was better after irradiation. However, there is one patient, who received radiation, with active disease 8 months after diagnosis. In stage

III tumors, no comparable observation supporting the impact of radiotherapy has been made.

A French study group reported on 27 adolescent and adult OSCCHT patients treated with a combination of cisplatin, Adriamycin, cyclophosphamide, and etoposide, then consolidated with high-dose chemotherapy and autologous stem cell transplantation. In this series that included four stage II, 14 stage II, and three stage IV patients, event-free survival was 34% and overall survival 49% (Pautier et al. 2007).

In the German pediatric series, the adjuvant chemotherapeutic regimens were heterogeneous and ranged from sarcoma (CEVAIE) to ovarian cancer (Carbo-Taxol) and germ cell tumor protocols (PEI). Response to chemotherapy was heterogeneous. The best results were achieved with sarcoma or germ cell tumor regimens, while classic ovarian carcinoma regimens were ineffective. Despite initial responses, six of eleven patients suffered recurrence. However, all five patients who underwent high-dose chemotherapy with autologous stem cell transplantation achieved long-term remission. The outcome of this series is comparable to that of the French series. Event-free survival is 0.28 ± 0.15 (4/11 patients), and 5-year survival is 0.49 ± 0.15 (6/11 patients) (Distelmaier et al. 2006b).

Based on this published experience, four additional patients have been treated with a combination of cisplatin, ifosfamide, and Adriamycin, followed by high-dose chemotherapy. All four currently remain in complete remission. Thus, combining all patients reported to the MAKEI registry, all nine patients treated with high-dose chemotherapy are alive and well, while all treated without high-dose chemotherapy have died from their tumor. On recurrence, OSCCHTs characteristically show a diffuse metastatic spread within the peritoneal cavity and involved abdominal and pelvic lymph nodes. A few patients may develop distant metastases to the liver and the skeletal system.

39.6.5 Approach to a Multimodal Therapy of OSCCHT of Children and Adolescents

In summary, the optimal management of OSCCHT still remains unknown. The only clear evidence is that after the diagnosis of OSCCHT, there is no role for expectant follow-up, even in completely resected stage Ia disease. Obviously, at least microscopic tumor spread has to be assumed in virtually all tumors, so that all require adjuvant therapy. It is also evident that adjuvant chemotherapy may successfully eradicate such subclinical disease, and according to the study by Harrison, Pautier, and the German series, a platin-based regimen that includes etoposide, alkylating agents, and anthracyclins currently appears to be the most promising combination regimen (Distelmaier et al. 2006b; Harrison et al. 2006; Pautier et al. 2007).

Preliminary information indicates that high-dose chemotherapy may indeed be useful in consolidating a complete clinical remission previously achieved with surgery and conventional chemotherapy. For locally intensive tumor control, either abdominal irradiation of locoregional hyperthermia may be considered (Distelmaier et al. 2006b; Harrison et al. 2006).

This positive development and the anticipation that more patients with OSCCHT will be registered in the future have encouraged the German MAKEI germ cell tumor study group to incorporate a therapeutic recommendation for patients with OSCCHT in the upcoming MAKEI protocol. Thus, further patients can hopefully be evaluated prospectively. According to this protocol, a timely histopathologic review of all ovarian tumors will be mandatory. In the case of an OSCCHT, all patients will receive adjuvant chemotherapy with a combination of cisplatin, ifosfamide, and Adriamycin for six cycles. Therapy will be completed with high-dose chemotherapy including carboplatin and etoposide, thus avoiding intolerably high cumulative doses of etoposide. In case of gross tumor residues after resection, a local deep hyperthermia will be discussed. The authors can be contacted for further details regarding therapy, and they would appreciate exchange of experience.

In conclusion, ovarian small cell carcinoma of the hypercalcemic type must still to be considered a prognostically unfavorable disease. However, data are accumulating, which open encouraging perspectives for cure through the use of adjuvant multiagent chemotherapy and consolidating high-dose chemotherapy. In addition, further genetic research on the biology of this rare neoplasm with recurrent familial clustering may uncover new therapeutic targets. However, these goals can only be achieved if patients are registered centrally and prospectively. The difficulty in collecting data from rare pediatric tumors must be emphasized. In the case of OSCCHT, clinicians often query experts on the appropriate treatment. Yet, scarce follow-up data are provided. These data might help inform future treatments, but the opportunity is lost without communication Thus, this

rare tumor type is an ideal candidate for international cooperation in order to achieve standardization of treatment and data collection in a registry ("Get friends!").

References

Overview on Epidemiology, Biology, Histology and Clinic

Afifi HY, Bosl GJ et al (1997) Mediastinal growing teratoma syndrome. Ann Thorac Surg 64(2):359–362

Altaras MM, Goldberg GL et al (1986) The value of cancer antigen-125 as a tumor marker in malignant germ cell tumors of the ovary. Gynecol Oncol 25(2):150–159

Atkin NB, Baker MC (1982) Specific chromosome change, i (12p), in testicular tumours? Lancet 2(8311):1349

Baranzelli MC, Kramar A et al (1999a) Prognostic factors in children with localized malignant nonseminomatous germ cell tumors. J Clin Oncol 17(4):1212

Belchis DA, Mowry J et al (1993) Infantile choriocarcinoma. Re-examination of a potentially curable entity. Cancer 72(6):2028–2032

Bernbeck B, Schneider DT et al (2009a) Germ cell tumors of the head and neck: report from the MAKEI Study Group. Pediatr Blood Cancer 52(2):223–226

Billmire DF, Grosfeld JL (1986) Teratomas in childhood: analysis of 142 cases. J Pediatr Surg 21(6):548–551

Blohm ME, Vesterling-Horner D et al (1998a) Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol 15(2):135–142

Bokemeyer C, Berger CC et al (1996) Evaluation of long-term toxicity after chemotherapy for testicular cancer. J Clin Oncol 14(11):2923–2932

Bosl GJ, Geller NL et al (1988) A randomized trial of etoposide + cisplatin versus vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin in patients with good-prognosis germ cell tumors. J Clin Oncol 6(8):1231–1238

Buetow SA (1995) Epidemiology of testicular cancer. Epidemiol Rev 17(2):433–449

Bussey KJ, Lawce HJ et al (1999a) Chromosome abnormalities of eighty-one pediatric germ cell tumors: sex-, age-, site-, and histopathology-related differences–a Children's Cancer Group study. Genes Chromosomes Cancer 25(2):134–146

Bussey KJ, Lawce HJ et al (2001) Chromosomes 1 and 12 abnormalities in pediatric germ cell tumors by interphase fluorescence in situ hybridization. Cancer Genet Cytogenet 125(2):112–118

Calaminus G, Schneider DT et al (2009) Survival after an anti-angiogenetic therapy and surgery in a wide spread growing teratoma originating from a testicular mixed malignant germ cell tumor. Klin Padiatr 221(3):136–140

Carver BS, Serio AM et al (2007a) Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol 25(35):5603–5608

Carver BS, Shayegan B et al (2007b) Incidence of metastatic nonseminomatous germ cell tumor outside the boundaries of a modified postchemotherapy retroperitoneal lymph node dissection. J Clin Oncol 25(28):4365–4369

Carver BS, Shayegan B et al (2007c) Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. J Clin Oncol 25(9):1033–1037

Chaganti RS, Rodriguez E et al (1994) Origin of adult male mediastinal germ-cell tumours. Lancet 343(8906):1130–1132

Cheng L, Roth LM et al (2010) KIT gene mutation and amplification in dysgerminoma of the ovary. Cancer 117(10):2096–2103

Clement PB, Young RH et al (1987) Endometrioid-like variant of ovarian yolk sac tumor. A clinicopathological analysis of eight cases. Am J Surg Pathol 11(10):767–778

Cohen MB, Friend DS et al (1987) Gonadal endodermal sinus (yolk sac) tumor with pure intestinal differentiation: a new histologic type. Pathol Res Pract 182(5):609–616

Cools M, Drop SL et al (2006) Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev 27(5):468–484

Cushing B, Giller R et al (2004a) Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a Pediatric Intergroup Study–Pediatric Oncology Group 9049 and Children's Cancer Group 888. J Clin Oncol 22(13): 2691–2700

Dal Cin P, Drochmans A et al (1989) Isochromosome 12p in mediastinal germ cell tumor. Cancer Genet Cytogenet 42(2):243–251

Dehner LP (1983a) Gonadal and extragonadal germ cell neoplasia of childhood. Hum Pathol 14(6):493–511

Doitsidou M, Reichman-Fried M et al (2002) Guidance of primordial germ cell migration by the chemokine SDF-1. Cell 111(5):647–659

Dolci S, Pesce M et al (1993) Combined action of stem cell factor, leukemia inhibitory factor, and cAMP on in vitro proliferation of mouse primordial germ cells. Mol Reprod Dev 35(2):134–139

Draper JS, Smith K et al (2004) Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells. Nat Biotechnol 22(1):53–54

Einhorn LH, Donohue J (1977a) Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87(3):293–298

Einhorn LH, Williams SD et al (1989a) Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 7(3):387–391

Einhorn LH, Williams SD et al (2007) High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 357(4):340–348

Fritsch MK, Schneider DT et al (2006) Activation of Wnt/beta-catenin signaling in distinct histologic subtypes of human germ cell tumors. Pediatr Dev Pathol 9(2):115–131

Gietema JA, Sleijfer DT et al (1992) Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated nonseminomatous testicular cancer. Ann Intern Med 116(9):709–715

Gilbert DC, Chandler I et al (2009) Clinical and biological significance of CXCL12 and CXCR4 expression in adult testes and germ cell tumours of adults and adolescents. J Pathol 217(1):94–102

Gitlin D, Perricelli A et al (1972) Synthesis of -fetoprotein by liver, yolk sac, and gastrointestinal tract of the human conceptus. Cancer Res 32(5):979–982

Göbel U, Calaminus G et al (1997a) Extracranial non-testicular teratoma in childhood and adolescence: introduction of a risk score for stratification of therapy. Klin Padiatr 209(4):228–234

Göbel U, Calaminus G et al (1998a) Teratomas in infancy and childhood. Med Pediatr Oncol 31(1):8–15

Göbel U, Schneider DT et al (2000a) Germ-cell tumors in childhood and adolescence. GPOH MAKEI and the MAHO study groups. Ann Oncol 11(3):263–271

Göbel U, Schneider DT et al (2001a) Multimodal treatment of malignant sacrococcygeal germ cell tumors: a prospective analysis of 66 patients of the German cooperative protocols MAKEI 83/86 and 89. J Clin Oncol 19(7):1943–1950

Godin I, Deed R et al (1991) Effects of the steel gene product on mouse primordial germ cells in culture. Nature 352(6338):807–809

Gonzalez-Crussi F, Winkler RF et al (1978) Sacrococcygeal teratomas in infants and children: relationship of histology and prognosis in 40 cases. Arch Pathol Lab Med 102(8):420–425

Group, I. G. C. C. C (1997a) International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 15(No 2 (February)):594–603

Harms D, Janig U (1986) Germ cell tumours of childhood. Report of 170 cases including 59 pure and partial yolk-sac tumours. Virchows Arch A Pathol Anat Histopathol 409(2):223–239

Harms D, Zahn S et al (2006a) Pathology and molecular biology of teratomas in childhood and adolescence. Klin Padiatr 218(6):296–302

Hartmann JT, Nichols CR et al (2000) Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. J Natl Cancer Inst 92(1):54–61

Hasle H, Mellemgaard A et al (1995) Cancer incidence in men with Klinefelter syndrome. Br J Cancer 71(2):416–420

Hawkins E, Perlman EJ (1996a) Germ cell tumors in childhood: morphology and biology. In: Parham DM (ed) Pediatric neoplasia: morphology and biology. Raven, New York, p 297

Hawkins EP (1990) Pathology of germ cell tumors in children. Crit Rev Oncol Hematol 10(2):165–179

Hawkins EP, Finegold MJ et al (1986) Nongerminomatous malignant germ cell tumors in children. A review of 89 cases from the Pediatric Oncology Group, 1971–1984. Cancer 58(12):2579–2584

Ho DM, Liu HC (1992) Primary intracranial germ cell tumor. Pathologic study of 51 patients. Cancer 70(6):1577–1584

Hoei-Hansen CE, Sehested A et al (2006) New evidence for the origin of intracranial germ cell tumours from primordial germ cells: expression of pluripotency and cell differentiation markers. J Pathol 209(1):25–33

Jenderny J, Koster E et al (1995) Detection of chromosome aberrations in paraffin sections of seven gonadal yolk sac tumors of childhood. Hum Genet 96(6):644–650

Kaatsch P (2004a) German childhood cancer registry and its favorable setting. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 47(5):437–443

Kaplan CG, Askin FB et al (1979a) Cytogenetics of extragonadal tumors. Teratology 19(2):261–266

Knight KR, Kraemer DF et al (2005) Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol 23(34):8588–8596

Koshida K, Nishino A et al (1991) The role of alkaline phosphatase isoenzymes as tumor markers for testicular germ cell tumors. J Urol 146(1):57–60

Kurman RJ, Norris HJ (1976a) Malignant mixed germ cell tumors of the ovary. A clinical and pathologic analysis of 30 cases. Obstet Gynecol 48(5):579–589

Lee SH, Appleby V et al (2010) Variable methylation of the imprinted gene, SNRPN, supports a relationship between intracranial germ cell tumours and neural stem cells. J Neurooncol 101(3):419–428

Li Y, Womer RB et al (2004) Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer 40(16):2445–2451

Logothetis CJ, Samuels ML et al (1985) Chemotherapy of extragonadal germ cell tumors. J Clin Oncol 3(3): 316–325

Looijenga LH, Stoop H et al (2003) POU5F1 (OCT3/4) identifies cells with pluripotent potential in human germ cell tumors. Cancer Res 63(9):2244–2250

Mann JR, Pearson D et al (1989a) Results of the United Kingdom Children's Cancer Study Group's malignant germ cell tumor studies. Cancer 63(9):1657–1667

Mann JR, Raafat F et al (2000). The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18(22):3809–3818

Mann JR, Raafat F et al (2000a) The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18(22):3809–3818

Marina NMM, London WB, Frazier AJ, Rescorla F, Billmire DF, Davis M, Perlman E, Giller R, Lauer S (2003) Amifostine does not protect against the ototoxicity associated with high-dose cisplatin, etoposide, and bleomycin (HD-PEB) in pediatric germ cell tumors (Abstract # 798). Proceedings ASCO, American Society of Clinical Oncology

Marina N, London WB et al (2006a) Prognostic factors in children with extragonadal malignant germ cell tumors: a pediatric intergroup study. J Clin Oncol 24(16):2544–2548

Marina NM, Cushing B et al (1999a) Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: A Pediatric Oncology Group/Children's Cancer Group Intergroup Study. J Clin Oncol 17(7):2137–2143

Mauz-Körholz C, Harms D et al (2000a) Primary chemotherapy and conservative surgery for vaginal yolk-sac tumour. Maligne Keimzelltumoren Study Group. Lancet 355(9204):625

Mayer F, Stoop H et al (2003a) Molecular determinants of treatment response in human germ cell tumors. Clin Cancer Res 9(2):767–773

Molyneaux KA, Zinszner H et al (2003) The chemokine SDF1/CXCL12 and its receptor CXCR4 regulate mouse germ cell migration and survival. Development 130(18): 4279–4286

Mostert M, Rosenberg C et al (2000) Comparative genomic and in situ hybridization of germ cell tumors of the infantile testis. Lab Invest 80(7):1055–1064

Motzer RJ, Mazumdar M et al (2000) Sequential dose-intensive paclitaxel, ifosfamide, carboplatin, and etoposide salvage therapy for germ cell tumor patients. J Clin Oncol 18(6):1173–1180

Nakashima N, Fukatsu T et al (1987) The frequency and histology of hepatic tissue in germ cell tumors. Am J Surg Pathol 11(9):682–692

Nichols CR, Heerema NA et al (1987a) Klinefelter's syndrome associated with mediastinal germ cell neoplasms. J Clin Oncol 5(8):1290–1294

Oldenburg J, Kraggerud SM et al (2007) Cisplatin-induced long-term hearing impairment is associated with specific glutathione s-transferase genotypes in testicular cancer survivors. J Clin Oncol 25(6):708–714

Oosterhuis JW, Looijenga LH (2005a) Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer 5(3):210–222

Oosterhuis JW, Rammeloo RH et al (1990) Ploidy of malignant mediastinal germ-cell tumors. Hum Pathol 21(7):729–732

Oosterhuis JW, Stoop H et al (2007) Why human extragonadal germ cell tumours occur in the midline of the body: old concepts, new perspectives. Int J Androl 30(4):256–263; discussion 263–264

Orazi A, Neiman RS et al (1993) Hematopoietic precursor cells within the yolk sac tumor component are the source of secondary hematopoietic malignancies in patients with mediastinal germ cell tumors. Cancer 71(12):3873–3881

Orth JM, Qiu J et al (1997) Expression of the c-kit gene is critical for migration of neonatal rat gonocytes in vitro. Biol Reprod 57(3):676–683

Osanto S, Bukman A et al (1992) Long-term effects of chemotherapy in patients with testicular cancer. J Clin Oncol 10(4):574–579

Palmer RD, Foster NA et al (2007) Malignant germ cell tumours of childhood: new associations of genomic imbalance. Br J Cancer 96(4):667–676

Palmer RD, Barbosa-Morais NL et al (2008) Pediatric malignant germ cell tumors show characteristic transcriptome profiles. Cancer Res 68(11):4239–4247

Palmer RD, Murray MJ et al (2010) Malignant germ cell tumors display common microRNA profiles resulting in global changes in expression of messenger RNA targets. Cancer Res 70(7):2911–2923

Perlman EJ, Cushing B et al (1994a) Cytogenetic analysis of childhood endodermal sinus tumors: a Pediatric Oncology Group study. Pediatr Pathol 14(4):695–708

Perlman EJ, Valentine MB et al (1996) Deletion of 1p36 in childhood endodermal sinus tumors by two-color fluorescence in situ hybridization: a pediatric oncology group study. Genes Chromosomes Cancer 16(1):15–20

Perlman EJ, Hu J et al (2000) Genetic analysis of childhood endodermal sinus tumors by comparative genomic hybridization. J Pediatr Hematol Oncol 22(2):100–105

Poynter JN, Amatruda JF et al (2010) Trends in incidence and survival of pediatric and adolescent patients with germ cell tumors in the United States, 1975 to 2006. Cancer 116(20): 4882–4891

Prall JA, McGavran L et al (1995) Intracranial malignant germ cell tumor and the Klinefelter syndrome. Case report and review of the literature. Pediatr Neurosurg 23(4): 219–224

Rapley EA, Hockley S et al (2004) Somatic mutations of KIT in familial testicular germ cell tumours. Br J Cancer 90(12):2397–2401

Riedemann L, Lanvers C et al (2008) Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. Pharmacogenomics J 8(1):23–28

Ries LAG SM, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) (1999a) Cancer incidence and survival among children and adolescents: United States SEER program 1975–1995. National Cancer Institute, Bethesda, SEER Program. NIH Publication No. 99–4649

Rodriguez E, Mathew S et al (1992) Cytogenetic analysis of 124 prospectively ascertained male germ cell tumors. Cancer Res 52(8):2285–2291

Rogers PC, Olson TA et al (2004a) Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: a Pediatric Intergroup Study–Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 22(17):3563–3569

Samaniego F, Rodriguez E et al (1990) Cytogenetic and molecular analysis of human male germ cell tumors: chromosome 12 abnormalities and gene amplification. Genes Chromosomes Cancer 1(4):289–300

Schmoll HJ, Kollmannsberger C, Metzner B, Hartmann JT, Schleucher N, Schoffski P, Schleicher J, Rick O, Beyer J, Hossfeld D, Kanz L, Berdel WE, Andreesen R, Bokemeyer C (2003) Long-term results of first-line sequential high-dose etoposide, ifosfamide, and cisplatin chemotherapy plus autologous stem cell support for patients with advanced metastatic germ cell cancer: an extended phase I/II study of the German Testicular Cancer Study Group. J Clin Oncol 21: 4083–4091

Schneider DT, Hilgenfeld E et al (1999) Acute myelogenous leukemia after treatment for malignant germ cell tumors in children. J Clin Oncol 17(10):3226–3233

Schneider DT, Calaminus G et al (2000a) Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. J Clin Oncol 18(4):832–839

Schneider DT, Calaminus G et al (2001a) Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. Pediatr Hematol Oncol 18(1): 11–26

Schneider DT, Schuster AE et al (2001b) Genetic analysis of childhood germ cell tumors with comparative genomic hybridization. Klin Padiatr 213(4):204–211

Schneider DT, Schuster AE et al (2001c) Multipoint imprinting analysis indicates a common precursor cell for gonadal and nongonadal pediatric germ cell tumors. Cancer Res 61(19):7268–7276

Schneider DT, Wessalowski R et al (2001d) Treatment of recurrent malignant sacrococcygeal germ cell tumors: analysis of 22 patients registered in the German protocols MAKEI 83/86, 89, and 96. J Clin Oncol 19(7):1951–1960

Schneider DT, Schuster AE et al (2002a) Genetic analysis of mediastinal nonseminomatous germ cell tumors in children and adolescents. Genes Chromosomes Cancer 34(1):115–125

Schneider DT, Calaminus G et al (2004a) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42(2):169–175

Schneider DT, Calaminus G et al (2005a) Ovarian sex cord-stromal tumors in children and adolescents. J Reprod Med 50(6):439–446
Schneider DT, Zahn S et al (2006) Molecular genetic analysis of central nervous system germ cell tumors with comparative genomic hybridization. Mod Pathol 19(6):864–873
Schwartz PE, Morris JM (1988) Serum lactic dehydrogenase: a tumor marker for dysgerminoma. Obstet Gynecol 72(3 Pt 2):511–515
Sievers S, Alemazkour K et al (2005a) IGF2/H19 imprinting analysis of human germ cell tumors (GCTs) using the methylation-sensitive single-nucleotide primer extension method reflects the origin of GCTs in different stages of primordial germ cell development. Genes Chromosomes Cancer 44(3):256–264
Silver SA, Wiley JM et al (1994) DNA ploidy analysis of pediatric germ cell tumors. Mod Pathol 7(9):951–956
Skakkebaek NE (2004) Testicular dysgenesis syndrome: new epidemiological evidence. Int J Androl 27(4):189–191
Skakkebaek NE, Holm M et al (2003) Association between testicular dysgenesis syndrome (TDS) and testicular neoplasia: evidence from 20 adult patients with signs of maldevelopment of the testis. APMIS 111(1):1–9; discussion 9–11
Talerman A (1987) Germ cell tumors of the ovary. In: Kurman RJ (ed) Blaustein's pathology of female genital tract. Springer, New York, p 659
Teilum G, Albrechtsen R et al (1975a) The histogenetic-embryologic basis for reappearance of alpha-fetoprotein in endodermal sinus tumors (yolk sac tumors) and teratomas. Acta Pathol Microbiol Scand A 83(1):80–86
Thomson JA, Itskovitz-Eldor J et al (1998) Embryonic stem cell lines derived from human blastocysts. Science 282(5391):1145–1147
Thurlbeck WM, Scully RE (1960) Solid teratoma of the ovary. A clinicopathological analysis of 9 cases. Cancer 13:804–811
Ulbright TM, Michael H et al (1990) Spindle cell tumors resected from male patients with germ cell tumors. A clinicopathologic study of 14 cases. Cancer 65(1):148–156
Ulbright TM, Roth LM (1987) Recent developments in the pathology of germ cell tumors. Semin Diagn Pathol 4(4):304–319
van den Belt-Dusebout AW, Nuver J et al (2006) Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 24(3):467–475
van der Gaast A, Kok TC et al (1991) Growing teratoma syndrome successfully treated with lymphoblastoid interferon. Eur Urol 19(3):257–258
van Echten J, Sleijfer DT et al (1997a) Cytogenetics of primary testicular nonseminoma, residual mature teratoma, and growing teratoma lesion in individual patients. Cancer Genet Cytogenet 96(1):1–6
van Echten J, van der Vloedt WS et al (1997b) Comparison of the chromosomal pattern of primary testicular nonseminomas and residual mature teratomas after chemotherapy. Cancer Genet Cytogenet 99(1):59–67
Vogelzang NJ, Lange PH et al (1982) Acute changes of alpha-fetoprotein and human chorionic gonadotropin during induction chemotherapy of germ cell tumors. Cancer Res 42(11):4855–4861
Wessalowski R, Blohm M et al (1997a) Treatment results in children and adolescents with loco-regional recurrences of abdominal germ cell tumors (GCTs): a pilot-study with PEI chemotherapy and regional deep hyperthermia (RHT) in comparison to a matched cohort. Klin Padiatr 209(4):250–256
Wessalowski R, Schneider DT et al (2003a) An approach for cure: PEI-chemotherapy and regional deep hyperthermia in children and adolescents with unresectable malignant tumors. Klin Padiatr 215(6):303–309
Young R, Scully R (1990a) Germ cell tumors: nonseminomatous tumors, occult tumors, effects of chemotherapy in testicular tumors. ASCP Press, Chicago
Yu IT, Griffin CA et al (1995) Numerical sex chromosomal abnormalities in pineal teratomas by cytogenetic analysis and fluorescence in situ hybridization. Lab Invest 72(4):419–423
Zahn S, Sievers S et al (2006) Imbalances of chromosome arm 1p in pediatric and adult germ cell tumors are caused by true allelic loss: a combined comparative genomic hybridization and microsatellite analysis. Genes Chromosomes Cancer 45(11):995–1006

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Alapetite C, Ricardi U, Saran F, Kortmann RD, Garre ML, Nicholson JC, Frappaz D, Göbel U, Patte C, Calaminus G (2002) Whole ventricular irradiation in combination with chemotherapy in intracranial germinoma: the Consensus of the SIOP CNS GCT Study Group. Med Pediatr Oncol 39:O114
Alapetite C, Brisse H, Patte C, Raquin MA, Gaboriaud G, Carrie C, Habrand JL, Thiesse P, Cuilliere JC, Bernier V, Ben-Hassel M, Frappaz D, Baranzelli MC, Bouffet E (2010) Pattern of relapse and outcome of non-metastatic germinoma patients treated with chemotherapy and limited field radiation: the SFOP experience. Neuro Oncol 12(12):1318–1325
Altman P, Randolph JG, Lilly JR (1974a) Sacrococcygeal teratoma: American Academy of Pediatrics surgical section survey-1973. J Pediatr Surg 9:389–398
Balmaceda C, Finlay J (2004) Current advances in the diagnosis and management of intracranial germ cell tumors. Curr Neurol Neurosci Rep 4:253–262
Balmaceda C, Heller G, Rosenblum M, Diez B, Villablanca JG, Kellie S, Maher P, Vlamis V, Walker RW, Leibel S, Finlay JL (1996) Chemotherapy without irradiation–a novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. The first international central nervous system germ cell tumor study. J Clin Oncol 14:2908–2915
Bamberg M, Kortmann RD, Calaminus G, Becker G, Meisner C, Harms D, Göbel U (1999) Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. J Clin Oncol 17:2585–2592
Baranzelli MC, Kramar A, Bouffet E, Quintana E, Rubie H, Edan C, Patte C (1999b) Prognostic factors in children with localized malignant nonseminomatous germ cell tumors. J Clin Oncol 17:1212–1219
Baranzelli MC, Bouffet E, Quintana E, Portas M, Thyss A, Patte C (2000a) Non-seminomatous ovarian germ cell tumours in children. Eur J Cancer 36:376–383

Bernbeck B, Schneider DT, Bernbeck B, Koch S, Teske C, Lentrodt J, Harms D, Göbel U, Calaminus G (2009b) Germ cell tumors of the head and neck: report from the MAKEI Study Group. Pediatr Blood Cancer 52:223–226

Billmire D, Vinocur C, Rescorla F, Colombani P, Cushing B, Hawkins E, Davis M, London WB, Lauer S, Giller R (2003) Malignant retroperitoneal and abdominal germ cell tumors: an intergroup study. J Pediatr Surg 38:315–318

Billmire D, Vinocur C, Rescorla F, Cushing B, London W, Schlatter M, Davis M, Giller R, Lauer S, Olson T (2004a) Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 39:424–429

Blohm ME, Vesterling-Hörner D, Calaminus G, Göbel U (1998b) Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol 15:135–142

Bokemeyer C, Schleucher N, Metzner B, Thomas M, Rick O, Schmoll HJ, Kollmannsberger C, Boehlke I, Kanz L, Hartmann JT (2003) First-line sequential high-dose VIP chemotherapy with autologous transplantation for patients with primary mediastinal nonseminomatous germ cell tumours: a prospective trial. Br J Cancer 89:29–35

Bryant WP, O'Marcaigh AS, Ledger GA, Zimmerman D (1994) Aqueous vasopressin infusion during chemotherapy in patients with diabetes insipidus. Cancer 74:2589–2592

Calaminus G, Vesterling-Hörner D, Bökkerink JP, Gadner H, Günther G, Haas HJ, Jürgens H, Teske C, Göbel U (1991) The prognostic significance of serum alpha 1-fetoprotein in children and adolescents with malignant extracranial nontesticular germ cell tumors. Klin Padiatr 203:246–250

Calaminus G, Bamberg M, Baranzelli MC, Benoit Y, Di MLC, Fossati-Bellani F, Jürgens H, Kühl HJ, Lenard HG, Lo CM, Göbel U (1994) Intracranial germ cell tumors: a comprehensive update of the European data. Neuropediatrics 25:26–32

Calaminus G, Andreussi L, Garre ML, Kortmann RD, Schober R, Göbel U (1997a) Secreting germ cell tumors of the central nervous system (CNS). First results of the cooperative German/Italian pilot study (CNS sGCT). Klin Padiatr 209:222–227

Calaminus G, Nicholson JC, Alapetite C, Bamberg M, Baranzelli MC, Frappaz D, Garre ML, Göbel U, Hale J, Kortmann RD, Mann JR, Patte C, Punt J, Ricardi U, Saran F, Harms D (2002) Malignant CNS Germ Cell Tumors (GCTs): interim analysis after 5 Years of SIOP CNS GCT 96. Med Pediatr Oncol 39:O030

Calaminus G, Schneider DT, Bökkerink JP, Gadner H, Harms D, Willers R, Göbel U (2003) Prognostic value of tumor size, metastases, extension into bone, and increased tumor marker in children with malignant sacrococcygeal germ cell tumors: a prospective evaluation of 71 patients treated in the German cooperative protocols Maligne Keimzelltumoren (MAKEI) 83/86 and MAKEI 89. J Clin Oncol 21:781–786

Calaminus G, Bamberg M, Harms D, Jürgens H, Kortmann RD, Sörensen N, Wiestler OD, Göbel U (2005) AFP/beta-HCG secreting CNS germ cell tumors: long-term outcome with respect to initial symptoms and primary tumor resection. Results of the cooperative trial MAKEI 89. Neuropediatrics 36:71–77

Chang CH, Housepian EM, Herbert CJ (1969) An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiology 93:1351–1359

Cho BK, Wang KC, Nam DH, Kim DG, Jung HW, Kim HJ, Han DH, Choi KS (1998) Pineal tumors: experience with 48 cases over 10 years. Childs Nerv Syst 14:53–58

Currarino G, Coln D, Votteler T (1981) Triad of anorectal, sacral, and presacral anomalies. AJR Am J Roentgenol 137:395–398

Cushing B, Giller R, Cullen JW, Marina NM, Lauer SJ, Olson TA, Rogers PC, Colombani P, Rescorla F, Billmire DF, Vinocur CD, Hawkins EP, Davis MM, Perlman EJ, London WB, Castleberry RP (2004b) Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study–Pediatric Oncology Group 9049 and Children's Cancer Group 888. J Clin Oncol 22:2691–2700

da Silva NS, Cappellano AM, Diez B, Cavalheiro S, Gardner S, Wisoff J, Kellie S, Parker R, Garvin J, Finlay J (2010) Primary chemotherapy for intracranial germ cell tumors: results of the third international CNS germ cell tumor study. Pediatr Blood Cancer 54:377–383

Dehner LP (1983b) Gonadal and extragonadal germ cell neoplasia of childhood. Hum Pathol 14:493–511

Diez B, Balmaceda C, Matsutani M, Weiner HL (1999) Germ cell tumors of the CNS in children: recent advances in therapy. Childs Nerv Syst 15:578–585

Draper H, Chitayat D, Ein SH, Langer JC (2009) Long-term functional results following resection of neonatal sacrococcygeal teratoma. Pediatr Surg Int 25:243–246

Esik O, Nemeth G, Szepeshazi K (1994) Calcitonin-secreting ovarian strumal carcinoid. Eur J Gynaecol Oncol 15: 211–216

Frazier AL, Rumcheva P, Olson T, Giller R, Cushing B, Cullen J, Marina N, London WB (2008) Application of the adult international germ cell classification system to pediatric malignant nonseminomatous germ cell tumors: a report from the Children's Oncology Group. Pediatr Blood Cancer 50:746–751

Ganjoo KN, Rieger KM, Kesler KA, Sharma M, Heilman DK, Einhorn LH (2000) Results of modern therapy for patients with mediastinal nonseminomatous germ cell tumors. Cancer 88:1051–1056

Garre ML, El-Hossainy MO, Fondelli P, Göbel U, Brisigotti M, Donati PT, Nantron M, Ravegnani M, Garaventa A, De BB (1996) Is chemotherapy effective therapy for intracranial immature teratoma? A case report. Cancer 77:977–982

Göbel U, Calaminus G, Blohm M, Booss D, Felberbauer F, Hofmann U, Holschneider AM, Willnow U, Harms D (1997b) Extracranial non-testicular teratoma in childhood and adolescence: introduction of a risk score for stratification of therapy. Klin Padiatr 209:228–234

Göbel U, Calaminus G, Waag K, Jonat W, Harms D (1998b) Extracranial non-testicular teratoma in childhood and adolescents-the German experience. Germ Cell Tumors IV:233–236

Göbel U, Calaminus G, Engert J, Kaatsch P, Gadner H, Bökkerink JP, Hass RJ, Waag K, Blohm ME, Dippert S, Teske C, Harms D (1998c) Teratomas in infancy and childhood. Med Pediatr Oncol 31:8–15

Göbel U, Gutjahr P, Jürgens H, Kabisch H, Lampert F, Spaar H-J, Sternschulte W (1999) Die kooperative Therapiestudie für nichttestikuläre Keimzelltumoen MAKEI83 der GPO: Analyse nach 3 Jahren. Klin Padiatr 198:237–244

Göbel U, Schneider DT, Calaminus G, Haas RJ, Schmidt P, Harms D (2000b) Germ-cell tumors in childhood and adolescence. Ann Oncol 11:263–271

Göbel U, Schneider DT, Calaminus G, Jurgens H, Spaar HJ, Sternschulte W, Waag K, Harms D (2001b) Multimodal treatment of malignant sacrococcygeal germ cell tumors: a prospective analysis of 66 patients of the German cooperative protocols MAKEI 83/86 and 89. J Clin Oncol 19:1943–1950

Hale J, Dang H, Krailo M, Olson T, Donachie P, Nicholson J, Billmire D, Thornton C, Frazier L (2010) Mediastinal germ cell tumors - are all patients high risk? Pediatr Blood Cancer 55:804

Harms D, Jänig U (1986) Germ cell tumours of childhood. Report of 170 cases including 59 pure and partial yolk-sac tumours. Virchows Arch A Pathol Anat Histopathol 409:223–239

Hieda S, Fukui T (2008) Germinoma presenting with personality and socio-behavioral abnormalities may challenge differential diagnoses. Brain Nerve 60:949–953

International-Germ-Cell-Cancer-Collaborative-Group (1997) International Germ Cell Consensus Classification: a prognostic factor- based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 15:594–603

Jelin E, Jelin AC, Lee H (2009) Sacrococcygeal teratoma with spinal canal invasion prenatally diagnosed. J Pediatr Surg 44:E9–E11

Kapoor G, Advani SH, Nair CN, Pai K, Kurkure PA, Nair R, Saikia TK, Vege D, Desai PB (1995) Pediatric germ cell tumor. An experience with BEP. J Pediatr Hematol Oncol 17:318–324

Kellie SJ, Boyce H, Dunkel IJ, Diez B, Rosenblum M, Brualdi L, Finlay JL (2004) Primary chemotherapy for intracranial nongerminomatous germ cell tumors: results of the second international CNS germ cell study group protocol. J Clin Oncol 22:846–853

Khatua S, Dhall G, O'Neil S, Jubran R, Villablanca JG, Marachelian A, Nastia A, Lavey R, Olch AJ, Gonzalez I, Gilles F, Nelson M, Panigrahy A, McComb G, Krieger M, Fan J, Sposto R, Finlay JL (2010) Treatment of primary CNS germinomatous germ cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation. Pediatr Blood Cancer 55:42–46

Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. Brain Pathol 3:255–268

Lam SK, Cheung LP (1996) Inappropriate ADH secretion due to immature ovarian teratoma. Aust N Z J Obstet Gynaecol 36:104–105

Lindahl H (1988) Giant sacrococcygeal teratoma: a method of simple intraoperative control of hemorrhage. J Pediatr Surg 23:1068–1069

Lopes LF, Chazan R, Sredni ST, de CB (1999) Endodermal sinus tumor of the vagina in children. Med Pediatr Oncol 32:377–381

Lopes LF, Sonaglio V, Ribeiro KC, Schneider DT, de CB (2008) Improvement in the outcome of children with germ cell tumors. Pediatr Blood Cancer 50:250–253

Lopes LF, Macedo CR, Pontes EM, Dos Santos Aguiar S, Mastellaro MJ, Melaragno R, Vianna SM, Lopes PA, Mendonca N, de Assis Almeida MT, Sonaglio V, Ribeiro KB, Santana VM, Schneider DT, de Camargo B (2009) Cisplatin and etoposide in childhood germ cell tumor: brazilian pediatric oncology society protocol GCT-91. J Clin Oncol 27:1297–1303

Lopes LF, Macedo CR, Pontes EM, Dos S, Aguiar S, Mastellaro MJ, Melaragno R, Vianna SM, Lopes PA, Mendonca N, de Assis Almeida MT, Sonaglio V, Ribeiro KB, Santana VM, Schneider DT, de Camargo B (2009a) Cisplatin and etoposide in childhood germ cell tumor: Brazilian pediatric oncology society protocol GCT-91. J Clin Oncol 27:1297–1303

Mann JR, Pearson D, Barrett A, Raafat F, Barnes JM, Wallendszus KR (1989b) Results of the United Kingdom Children's Cancer Study Group's malignant germ cell tumor studies. Cancer 63:1657–1667

Mann JR, Raafat F, Robinson K, Imeson J, Gornall P, Phillips M, Sokal M, Gray E, McKeever P, Oakhill A (1998) UKCCSG's germ cell tumour (GCT) studies: improving outcome for children with malignant extracranial non-gonadal tumours–carboplatin, etoposide, and bleomycin are effective and less toxic than previous regimens. United Kingdom Children's Cancer Study Group. Med Pediatr Oncol 30:217–227

Mann JR, Raafat F, Robinson K, Imeson J, Gornall P, Sokal M, Gray E, McKeever P, Hale J, Bailey S, Oakhill A (2000b) The United Kingdom Children's Cancer Study Group's Second Germ Cell Tumor Study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18:3809–3818

Mann JR, Gray ES, Thornton C, Raafat F, Robinson K, Collins GS, Gornall P, Huddart SN, Hale JP, Oakhill A (2008a) Mature and immature extracranial teratomas in children: the UK Children's Cancer Study Group Experience. J Clin Oncol 26:3590–3597

Marina NM, Cushing B, Giller R, Cohen L, Lauer SJ, Ablin A, Weetman R, Cullen J, Rogers P, Vinocur C, Stolar C, Rescorla F, Hawkins E, Heifetz S, Rao PV, Krailo M, Castleberry RP (1999b) Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: a Pediatric Oncology Group/Children's Cancer Group Intergroup Study. J Clin Oncol 17:2137

Mauz-Körholz C, Harms D, Calaminus G, Göbel U (2000b) Primary chemotherapy and conservative surgery for vaginal yolk-sac tumour. Maligne Keimzelltumoren Study Group. Lancet 355:625

Mayer F, Stoop H, Scheffer GL, Scheper R, Oosterhuis JW, Looijenga LH, Bokemeyer C (2003b) Molecular determinants of treatment response in human germ cell tumors. Clin Cancer Res 9:767–773

Mostofi FK, Sobin LH (1993) Histopathological typing of testis tumors. World Health Organization, Geneva

Nichols CR, Heerema NA, Palmer C, Loehrer PJ Sr, Williams SD, Einhorn LH (1987b) Klinefelter's syndrome associated with mediastinal germ cell neoplasms. J Clin Oncol 5:1290–1294

Nicholson JC, Punt J, Hale J, Saran F, Calaminus G (2002) Neurosurgical management of paediatric germ cell tumours of the central nervous system–a multi-disciplinary team approach for the new millennium. Br J Neurosurg 16:93–95

Oosterhuis JW, Looijenga LH (2005b) Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer 5:210–222

Rescorla FJ (2008) Malignant germ cell tumors. In: Carachi R, Grosfeld JL, Azmy AF (eds) The surgery of childhood tumors. Springer, New York, pp 261–273

Ribeiro PR, Guys JM, Lena G (1999) Sacrococcygeal teratoma with an intradural and extramedullary extension in a neonate: case report. Neurosurgery 44:398–400

Rogers PC, Olson TA, Cullen JW, Billmire DF, Marina N, Rescorla F, Davis MM, London WB, Lauer SJ, Giller RH, Cushing B (2004b) Treatment of children and adolescents with stage II testicular and stage I and II ovarian malignant germ cell tumors: a Pediatric Intergroup Study–Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 22:3563–3569

Schmoll HJ, Kollmannsberger C, Metzner B, Hartmann JT, Schleucher N, Schoffski P, Schleicher J, Rick O, Beyer J, Hossfeld D, Kanz L, Berdel WE, Andreesen R, Bokemeyer C (2003) Long-term results of first-line sequential high-dose etoposide, ifosfamide, and cisplatin chemotherapy plus autologous stem cell support for patients with advanced metastatic germ cell cancer: an extended phase I/II study of the German Testicular Cancer Study Group. J Clin Oncol 21:4083–4091

Schneider DT, Calaminus G, Reinhard H, Gutjahr P, Kremens B, Harms D, Göbel U (2000b) Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. J Clin Oncol 18:832–839

Schneider DT, Calaminus G, Göbel U (2001e) Diagnostic value of alpha_1_-fetoprotein and human chorionic gonadotropic hormone in infancy and childhood. Pediatr Hematol Oncol 18:11–26

Schneider DT, Wessalowski R, Calaminus G, Pape H, Bamberg M, Engert J, Waag K, Gadner H, Göbel U (2001f) Treatment of recurrent malignant sacrococcygeal germ cell tumors: analysis of 22 patients registered in the German protocols makei 83/86, 89, and 96. J Clin Oncol 19:1951–1960

Schneider DT, Schuster AE, Fritsch MK, Calaminus G, Göbel U, Harms D, Lauer S, Olson T, Perlman EJ (2002b) Genetic analysis of mediastinal nonseminomatous germ cell tumors in children and adolescents. Genes Chromosomes Cancer 34:115–125

Schneider DT, Calaminus G, Koch S, Teske C, Schmidt P, Haas RJ, Harms D, Göbel U (2004b) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42:169–175

Schwabe J, Francke A, Gerharz CD, Willnow U, Schneider DT, Nürnberger W (2000) Immature teratoma arising from an intra-abdominal testis in a 5-month-old boy. Med Pediatr Oncol 35:140–141

Serov SF, Scully RE (1973) Histological typing of ovarian tumors. World Health Organization, Geneva

Teilum G, Albrechtsen R, Norgaard-Pedersen B (1975b) The histogenetic-embryologic basis for reappearance of alpha-fetoprotein in endodermal sinus tumors (yolk sac tumors) and teratomas. Acta Pathol Microbiol Scand A 83:80–86

Wessalowski R, Blohm M, Calaminus G, Engert J, Harms D, Krause I, Kruck H, Grüttner HP, Pape H, Göbel U (1997b) Treatment results in children and adolescents with locoregional recurrences of abdominal germ cell tumors (GCTs): a pilot-study with PEI chemotherapy and regional deep hyperthermia (RHT) in comparison to a matched cohort. Klin Padiatr 209:250–256

Wessalowski R, Schneider DT, Mils O, Hannen M, Calaminus G, Engelbrecht V, Pape H, Willers R, Engert J, Harms D, Göbel U (2003b) An approach to cure: PEI chemotherapy and regional deep hyperthermia in children and adolescents with unresectable malignant tumors. Klin Padiatr 215:303–309

Yassa L, Sadow P, Marqusee E (2008) Malignant struma ovarii. Nat Clin Pract Endocrinol Metab 4:469–472

Young RH (2005a) A brief history of the pathology of the gonads. Mod Pathol 18(Suppl 2):S3–S17

Testicular Germ Cell tumors

Altman RP, Randolph JG et al (1974b) Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey-1973. J Pediatr Surg 9(3):389–398

Atkin NB, Baker MC (1992) X-chromatin, sex chromosomes, and ploidy in 37 germ cell tumors of the testis. Cancer Genet Cytogenet 59(1):54–56

Baranzelli MC, Patte C (1998) The french experience in paediatric malignant germ cell tumours. In: Jones WG, Appleyard I, Harnden P, Joffe JK (eds) Germ cell tumours IV. John Libbey and Co. Ltd, London, pp 219–226

Baranzelli MC, Kramar A et al (1999c) Prognostic factors in children with localized malignant nonseminomatous germ cell tumors. J Clin Oncol 17(4):1212

Billmire DF (2006a) Malignant germ cell tumors in childhood. Semin Pediatr Surg 15(1):30–36

Bussey KJ, Lawce HJ et al (1999b) Chromosome abnormalities of eighty-one pediatric germ cell tumors: sex-, age-, site-, and histopathology-related differences–a Children's Cancer Group study. Genes Chromosomes Cancer 25(2): 134–146

Carver BS, Motzer RJ et al (2005) Late relapse of testicular germ cell tumors. Urol Oncol 23(6):441–445

Carver BS, Shayegan B et al (2007d) Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. J Clin Oncol 25(9):1033–1037

Cushing B, Giller R et al (2004c) Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose Cisplatin in children and adolescents with high-risk malignant germ cell tumors: a Pediatric Intergroup Study–Pediatric Oncology Group 9049 and Children's Cancer Group 888. J Clin Oncol 22(13):2691–2700

Einhorn LH, Donohue J (1977b) Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87(3): 293–298

Einhorn LH, Williams SD et al (1989b) Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 7(3):387–391

el-Naggar AK, Ro JY et al (1992) DNA ploidy in testicular germ cell neoplasms. Histogenetic and clinical implications. Am J Surg Pathol 16(6):611–618

Giwercman A, Grindsted J et al (1987) Testicular cancer risk in boys with maldescended testis: a cohort study. J Urol 138(5):1214–1216

Göbel U, Calaminus G et al (2002a) Management of germ cell tumors in children: approaches to cure. Onkologie 25(1):14–22
Göbel U, Haas RJ et al (1990) Treatment of germ cell tumors in children: results of European trials for testicular and non-testicular primary sites. Crit Rev Oncol Hematol 10(2):89–98
Group, I. G. C. C. C (1997b) International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 15(No 2 (February)):594–603
Haas RJ, Schmidt P et al (1999) Testicular germ cell tumors, an update. Results of the German cooperative studies 1982–1997. Klin Padiatr 211(4):300–304
Harms D, Zahn S et al (2006b) Pathology and molecular biology of teratomas in childhood and adolescence. Klin Padiatr 218(6):296–302
Hawkins E, Perlman EJ (1996b) Germ cell tumors in childhood: morphology and biology. In: Parham DM (ed) Pediatric neoplasia: morphology and biology. Raven, New York, p 297
Kaatsch P (2004b) German Childhood Cancer Registry and its favorable setting. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 47(5):437–443
Kaplan CG, Askin FB et al (1979b) Cytogenetics of extragonadal tumors. Teratology 19(2):261–266
Kurman RJ, Norris HJ (1976b) Malignant mixed germ cell tumors of the ovary. A clinical and pathologic analysis of 30 cases. Obstet Gynecol 48(5):579–589
Lo Curto M, Lumia F et al (2003) Malignant germ cell tumors in childhood: results of the first Italian cooperative study "TCG 91". Med Pediatr Oncol 41(5):417–425
Looijenga LH, Gillis AJ et al (1993) In situ numeric analysis of centromeric regions of chromosomes 1, 12, and 15 of seminomas, nonseminomatous germ cell tumors, and carcinoma in situ of human testis. Lab Invest 68(2):211–219
Lopes LF, Macedo CR et al (2009b) Cisplatin and etoposide in childhood germ cell tumor: Brazilian pediatric oncology society protocol GCT-91. J Clin Oncol 27(8):1297–1303
Mann JR, Gray ES et al (2008b) Mature and immature extracranial teratomas in children: the UK Children's Cancer Study Group Experience. J Clin Oncol 26(21):3590–3597
Mann JR, Raafat F et al (2000c) The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18(22):3809–3818
Marina N, Chang KW et al (2005) Amifostine does not protect against the ototoxicity of high-dose cisplatin combined with etoposide and bleomycin in pediatric germ-cell tumors: a Children's Oncology Group study. Cancer 104(4):841–847
Marina NM, Cushing B et al (1999c) Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: a Pediatric Oncology Group/Children's Cancer Group Intergroup Study. J Clin Oncol 17(7):2137–2143
Marina N, London WB et al (2006b) Prognostic factors in children with extragonadal malignant germ cell tumors: a pediatric intergroup study. J Clin Oncol 24(16):2544–2548
Mostert MM, van de Pol M et al (1996) Comparative genomic hybridization of germ cell tumors of the adult testis: confirmation of karyotypic findings and identification of a 12p-amplicon. Cancer Genet Cytogenet 89(2):146–152
Oosterhuis JW, Castedo SM et al (1988) Karyotyping and DNA flow cytometry of an orchidoblastoma. Cancer Genet Cytogenet 36(1):7–11
Oosterhuis JW, Castedo SM et al (1989) Ploidy of primary germ cell tumors of the testis. Pathogenetic and clinical relevance. Lab Invest 60(1):14–21
Ozols RF, Ihde DC et al (1988) A randomized trial of standard chemotherapy v a high-dose chemotherapy regimen in the treatment of poor prognosis nonseminomatous germ-cell tumors. J Clin Oncol 6(6):1031–1040
Perlman EJ, Cushing B et al (1994b) Cytogenetic analysis of childhood endodermal sinus tumors: a Pediatric Oncology Group study. Pediatr Pathol 14(4):695–708
Ries LAG SM, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) (1999b) Cancer incidence and survival among children and adolescents: United States SEER program 1975–1995. National Cancer Institute, Bethesda, National Cancer Institute, SEER Program. NIH Publication No. 99–4649
Rodriguez E, Houldsworth J et al (1993) Molecular cytogenetic analysis of i (12p)-negative human male germ cell tumors. Genes Chromosomes Cancer 8(4):230–236
Rogers PC, Olson TA et al (2004c) Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: a Pediatric Intergroup Study–Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 22(17):3563–3569
Schlatter M, Rescorla F et al (2003) Excellent outcome in patients with stage I germ cell tumors of the testes: a study of the Children's Cancer Group/Pediatric Oncology Group. J Pediatr Surg 38(3):319–324; discussion 319–324
Schmidt P, Haas RJ et al (2002a) Results of the German Studies (MAHO) for treatment of Testicular Germ Cell Tumors in Children - an update. Klin Padiatr 214(4):167–172
Schneider DT, Calaminus G et al (2004c) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42(2):169–175
Sievers S, Alemazkour K et al (2005b) IGF2/H19 imprinting analysis of human germ cell tumors (GCTs) using the methylation-sensitive single-nucleotide primer extension method reflects the origin of GCTs in different stages of primordial germ cell development. Genes Chromosomes Cancer 44(3):256–264
Stock C, Ambros IM et al (1994) Detection of numerical and structural chromosome abnormalities in pediatric germ cell tumors by means of interphase cytogenetics. Genes Chromosomes Cancer 11(1):40–50
van Gurp RJ, Oosterhuis JW et al (1994) Biallelic expression of the H19 and IGF2 genes in human testicular germ cell tumors. J Natl Cancer Inst 86(14):1070–1075
Young R, Scully R (1990b) Germ cell tumors: nonseminomatous tumors, occult tumors, effects of chemotherapy in testicular tumors. ASCP Press, Chicago

Germ Cell Tumors of the Ovary

Bagolan P, Rivosecchi M et al (1992) Prenatal diagnosis and clinical outcome of ovarian cysts. J Pediatr Surg 27(7):879–881
Baranzelli MC, Bouffet E et al (2000b) Non-seminomatous ovarian germ cell tumours in children. Eur J Cancer 36(3):376–383

Bernstein L, Smith MA et al (1999) Germ cell, trophoblastic and other gonadal neoplasms. In: Ries LAG SM, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. National Cancer Institute, Bethesda, Cancer Statistics Bran, Cancer Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute. NIH Pub. No. 99–4649.: 125–138

Billmire D, Vinocur C et al (2004b) Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 39(3):424–429; discussion 424–429

Billmire DF (2006b) Malignant germ cell tumors in childhood. Semin Pediatr Surg 15(1):30–36

Cannistra SA (1993) Cancer of the ovary. N Engl J Med 329:1550

Cass DL, Hawkins E et al (2001) Surgery for ovarian masses in infants, children, and adolescents: 102 consecutive patients treated in a 15-year period. J Pediatr Surg 36(5):693–699

Cronen PW, Nagaraj HS (1988) Ovarian tumors in children. South Med J 81(4):464–468

Cushing B, Giller R et al (2004d) Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a Pediatric Intergroup Study–Pediatric Oncology Group 9049 and Children's Cancer Group 888. J Clin Oncol 22(13):2691–2700

dos Santos Silva I, Swerdlow AJ (1991) Ovarian germ cell malignancies in England: epidemiological parallels with testicular cancer. Br J Cancer 63(5):814–818

Ehrlich PF, Teitelbaum DH et al (2007) Excision of large cystic ovarian tumors: combining minimal invasive surgery techniques and cancer surgery–the best of both worlds. J Pediatr Surg 42(5):890–893

Gibas Z, Talerman A et al (1993) Cytogenetic analysis of an immature teratoma of the ovary and its metastasis after chemotherapy-induced maturation. Int J Gynecol Pathol 12(3):276–280

Göbel U, Calaminus G et al (1998d) Teratomas in infancy and childhood. Med Pediatr Oncol 31(1):8–15

Göbel U, Calaminus G et al (2002b) Management of germ cell tumors in children: approaches to cure. Onkologie 25(1):14–22

Göbel U, Calaminus G et al (2006) The malignant potential of teratomas in infancy and childhood: the MAKEI experiences in non-testicular teratoma and implications for a new protocol. Klin Padiatr 218(6):309–314

Gribbon M, Ein SH et al (1992) Pediatric malignant ovarian tumors: a 43-year review. J Pediatr Surg 27(4):480–484

Harris BH, Boles ET Jr (1974) Rational surgery for tumors of the ovary in children. J Pediatr Surg 9(3):289–293

Hayes-Jordan A (2005) Surgical management of the incidentally identified ovarian mass. Semin Pediatr Surg 14(2):106–110

Hoffner L, Deka R et al (1994) Cytogenetics and origins of pediatric germ cell tumors. Cancer Genet Cytogenet 74(1):54–58

Jabra AA, Fishman EK et al (1993) Primary ovarian tumors in the pediatric patient: CT evaluation. Clin Imaging 17(3):199–203

King ME, DiGiovanni LM et al (1990) Immature teratoma of the ovary grade 3, with karyotype analysis. Int J Gynecol Pathol 9(2):178–184

Lovvorn HN 3rd, Tucci LA et al (1998) Ovarian masses in the pediatric patient. AORN J 67(3):568–576; quiz 577, 580–84

Mann JR, Pearson D et al (1989c) Results of the United Kingdom Children's Cancer Study Group's malignant germ cell tumor studies. Cancer 63(9):1657–1667

Mann JR, Raafat F et al (2000d) The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 18(22): 3809–3818

Mann JR, Gray ES et al (2008c) Mature and immature extracranial teratomas in children: the UK Children's Cancer Study Group Experience. J Clin Oncol 26(21):3590–3597

Marina NM, Pratt CB et al (1992) Improved prognosis of children with osteosarcoma metastatic to the lung (s) at the time of diagnosis. Cancer 70(11):2722–2727

Norris HJ, Zirkin HJ et al (1976) Immature (malignant) teratoma of the ovary: a clinical and pathologic study of 58 cases. Cancer 37(5):2359–2372

Ohama K, Nomura K et al (1985) Origin of immature teratoma of the ovary. Am J Obstet Gynecol 152(7 Pt 1): 896–900

Parrington JM, West LF et al (1984) The origin of ovarian teratomas. J Med Genet 21(1):4–12

Pienkowski C, Baunin C et al (2004) Ovarian masses in adolescent girls. Endocr Dev 7:163–182

Riopel MA, Spellerberg A et al (1998) Genetic analysis of ovarian germ cell tumors by comparative genomic hybridization. Cancer Res 58(14):3105–3110

Rogers PC, Olson TA et al (2004d) Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: a Pediatric Intergroup Study–Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 22(17):3563–3569

Schmidt P, Haas RJ et al (2002b) Results of the German Studies (MAHO) for treatment of Testicular Germ Cell Tumors in Children - an update. Klin Padiatr 214(4):167–172

Schneider DT, Schuster AE et al (2001g) Multipoint imprinting analysis indicates a common precursor cell for gonadal and nongonadal pediatric germ cell tumors. Cancer Res 61(19):7268–7276

Schultz KA, Sencer SF et al (2005) Pediatric ovarian tumors: a review of 67 cases. Pediatr Blood Cancer 44(2):167–173

Speleman F, De Potter C et al (1990) i (12p) in a malignant ovarian tumor. Cancer Genet Cytogenet 45(1):49–53

Surratt JT, Siegel MJ (1991) Imaging of pediatric ovarian masses. Radiographics 11(4):533–548

Surti U, Hoffner L et al (1990) Genetics and biology of human ovarian teratomas. I. Cytogenetic analysis and mechanism of origin. Am J Hum Genet 47(4):635–643

Templeman CL, Fallat ME (2005) Benign ovarian masses. Semin Pediatr Surg 14(2):93–99

Thompson FH, Emerson J et al (1994) Clonal chromosome abnormalities in 54 cases of ovarian carcinoma. Cancer Genet Cytogenet 73(1):33–45

Walker AH, Ross RK et al (1988) Hormonal factors and risk of ovarian germ cell cancer in young women. Br J Cancer 57(4):418–422

Sex Cord Stromal Tumors of the Testis and Ovary

Al-Agha OM, Huwait HF, Chow C, Yang W, Senz J, Kalloger SE, Huntsman DG, Young RH, Gilks CB (2011) FOXL2 is a sensitive and specific marker for sex cord-stromal tumors of the ovary. Am J Surg Pathol 35:484–494

Boyer A, Paquet M, Lague MN, Hermo L, Boerboom D (2009) Dysregulation of WNT/CTNNB1 and PI3K/AKT signaling in testicular stromal cells causes granulosa cell tumor of the testis. Carcinogenesis 30:869–878

Calaminus G, Wessalowski R, Harms D, Göbel U (1997b) Juvenile granulosa cell tumors of the ovary in children and adolescents: results from 33 patients registered in a prospective cooperative study. Gynecol Oncol 65:447–452

Cecchetto G, Alaggio R, Bisogno G, Virgone C, Dall'Igna P, Terenziani M, Boldrini R, D'Onofrio V, Ferrari A, Bernini G (2010) Sex cord-stromal tumors of the testis in children. A clinicopathologic report from the Italian TREP project. J Pediatr Surg 45:1868–1873

Cecchetto G, Ferrari A, Bernini G, Alaggio R, Collini P, Virgone C, Terenziani M, Dall'igna P, Cozza R, Conte M, Bisogno G (2011) Sex cord stromal tumors of the ovary in children: a clinicopathological report from the Italian TREP project. Pediatr Blood Cancer 56(7):1062–1067

Chang B, Borer JG, Tan PE, Diamond DA (1998) Large-cell calcifying Sertoli cell tumor of the testis: case report and review of the literature. Urology 52:520–522

Clement PB, Young RH, Scully RE (1991) Clinical syndromes associated with tumors of the female genital tract. Semin Diagn Pathol 8:204–233

Colombo N, Sessa C, Landoni F, Sartori E, Pecorelli S, Mangioni C (1986) Cisplatin, vinblastine, and bleomycin combination chemotherapy in metastatic granulosa cell tumor of the ovary. Obstet Gynecol 67:265–268

Crofton PM, Evans AE, Groome NP, Taylor MR, Holland CV, Kelnar CJ (2002a) Dimeric inhibins in girls from birth to adulthood: relationship with age, pubertal stage, FSH and oestradiol. Clin Endocrinol (Oxf) 56:223–230

Crofton PM, Evans AE, Groome NP, Taylor MR, Holland CV, Kelnar CJ (2002b) Inhibin B in boys from birth to adulthood: relationship with age, pubertal stage, FSH and testosterone. Clin Endocrinol (Oxf) 56:215–221

Distelmaier F, Calaminus G, Harms D, Sträter R, Cordes U, Fleischhack G, Göbel U, Schneider DT (2006a) Ovarian small cell carcinoma of the hypercalcemic type in children and adolescents: a prognostically unfavorable but curable disease. Cancer 107(9):2298–2306

Harms D, Kock LR (1997) Testicular juvenile granulosa cell and Sertoli cell tumours: a clinicopathological study of 29 cases from the Kiel Paediatric Tumour Registry. Virchows Arch 430:301–309

Hill DA, Ivanovich J, Priest JR, Gurnett CA, Dehner LP, Desruisseau D, Jarzembowski JA, Wikenheiser-Brokamp KA, Suarez BK, Whelan AJ, Williams G, Bracamontes D, Messinger Y, Goodfellow PJ (2009) DICER1 mutations in familial pleuropulmonary blastoma. Science 325:965

Jacoby AF, Young RH, Colvin RB, Flotte TJ, Preffer F, Scully RE, Swymer CM, Bell DA (1992) DNA content in juvenile granulosa cell tumors of the ovary: a study of early and advanced stage disease. Gynecol Oncol 46:97–103

Kalfa N, Patte C, Orbach D, Lecointre C, Pienkowski C, Philippe F, Thibault E, Plantaz D, Brauner R, Rubie H, Guedj AM, Ecochard A, Paris F, Jeandel C, Baldet P, Sultan C (2005) A nationwide study of granulosa cell tumors in pre- and post-pubertal girls: missed diagnosis of endocrine manifestations worsens prognosis. J Pediatr Endocrinol Metab 18:25–31

Kalfa N, Ecochard A, Patte C, Duvillard P, Audran F, Pienkowski C, Thibaud E, Brauner R, Lecointre C, Plantaz D, Guedj AM, Paris F, Baldet P, Lumbroso S, Sultan C (2006) Activating mutations of the stimulatory g protein in juvenile ovarian granulosa cell tumors: a new prognostic factor? J Clin Endocrinol Metab 91:1842–1847

Kalfa N, Fellous M, Boizet-Bonhoure B, Patte C, Duvillard P, Pienkowski C, Jaubert F, Ecochard A, Sultan C (2008) Aberrant expression of ovary determining gene FOXL2 in the testis and juvenile granulosa cell tumor in children. J Urol 180:1810–1813

Kim GJ, Georg I, Scherthan H, Merkenschlager M, Guillou F, Scherer G, Barrionuevo F (2010) Dicer is required for Sertoli cell function and survival. Int J Dev Biol 54:867–875

Kudelka AP, Vasuratna A, Edwards CL, Augustine K, Benjapibal M, Verschraegen CF, Kavanagh JJ (1998) Gemcitabine after bone marrow transplantation for refractory juvenile granulosa cell tumor. Anticancer Drugs 9:621–623

Plantaz D, Flamant F, Vassal G, Chappuis JP, Baranzelli MC, Bouffet E, Dyon JF, Armari C, Bost M (1992) Granulosa cell tumors of the ovary in children and adolescents. Multicenter retrospective study in 40 patients aged 7 months to 22 years. Arch Fr Pediatr 49:793–798

Poiana C, Virtej I, Carsote M, Banceanu G, Sajin M, Stanescu B, Ioachim D, Hortopan D, Coculescu M (2010) Virilising Sertoli-Leydig cell tumour associated with thyroid papillary carcinoma: case report and general considerations. Gynecol Endocrinol 26:617–622

Powell JL, Otis CN (1997) Management of advanced juvenile granulosa cell tumor of the ovary. Gynecol Oncol 64:282–284

Powell JL, Johnson NA, Bailey CL, Otis CN (1993) Management of advanced juvenile granulosa cell tumor of the ovary. Gynecol Oncol 48:119–123

Powell JL, Connor GP, Henderson GS (2001) Management of recurrent juvenile granulosa cell tumor of the ovary. Gynecol Oncol 81:113–116

Rio Frio T, Bahubeshi A, Kanellopoulou C, Hamel N, Niedziela M, Sabbaghian N, Pouchet C, Gilbert L, O'Brien PK, Serfas K, Broderick P, Houlston RS, Lesueur F, Bonora E, Muljo S, Schimke RN, Bouron-Dal Soglio D, Arseneau J, Schultz KA, Priest JR, Nguyen VH, Harach HR, Livingston DM, Foulkes WD, Tischkowitz M (2011) DICER1 mutations in familial multinodular goiter with and without ovarian Sertoli-Leydig cell tumors. JAMA 305:68–77

Ross JH, Rybicki L, Kay R (2002) Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. J Urol 168:1675–1678

Schneider DT, Calaminus G, Göbel U (2001h) Diagnostic value of alpha_1_-fetoprotein and human chorionic gonadotropic hormone in infancy and childhood. Pediatr Hematol Oncol 18:11–26

Schneider DT, Calaminus G, Wessalowski R, Pathmanathan R, Harms D, Göbel U (2002c) Therapy of advanced ovarian juvenile granulosa cell tumors. Klin Padiatr 214:173–178

Schneider DT, Calaminus G, Wessalowski R, Pathmanathan R, Selle B, Sternschulte W, Harms D, Göbel U (2003a) Ovarian sex cord-stromal tumors in children and adolescents. J Clin Oncol 21:2357–2363

Schneider DT, Jänig U, Calaminus G, Göbel U, Harms D (2003b) Ovarian sex cord - stromal tumors - A clinicopathologic study of 72 cases from the Kiel Pediatric Tumor Registry. Virchows Arch 443:549–560

Schmidt D, Ovitt CE, Anlag K, Fehsenfeld S, Gredsted L, Treier AC, Treier M (2004) The murine winged-helix transcription factor Foxl2 is required for granulosa cell differentiation and ovary maintenance. Development 131:933–942

Schneider DT, Calaminus G, Göbel U (2004d) Tumor rupture and mitotic index in pediatric sex cord-stromal tumors. J Clin Oncol 22:2033–2035

Schneider DT, Calaminus G, Harms D, Göbel U (2005b) Ovarian sex cord-stromal tumors in children and adolescents. J Reprod Med 50:439–446

Schneider DT, Orbach D, Cecchetto G, Stachowicz-Stenzel T, Calaminus G, Brummel B, Bisogno G, Patte C (2010) Sertoli-leydig cell tumors: an analysis of the European Cooperative Study Group on Pediatric Rare Tumors (eXpert). Pediatr Blood Cancer 55(5):909–909

Shah SP, Kobel M, Senz J, Morin RD, Clarke BA, Wiegand KC, Leung G, Zayed A, Mehl E, Kalloger SE, Sun M, Giuliany R, Yorida E, Jones S, Varhol R, Swenerton KD, Miller D, Clement PB, Crane C, Madore J, Provencher D, Leung P, DeFazio A, Khattra J, Turashvili G, Zhao Y, Zeng T, Glover JN, Vanderhyden B, Zhao C, Parkinson CA, Jimenez-Linan M, Bowtell DD, Mes-Masson AM, Brenton JD, Aparicio SA, Boyd N, Hirst M, Gilks CB, Marra M, Huntsman DG (2009) Mutation of FOXL2 in granulosa-cell tumors of the ovary. N Engl J Med 360:2719–2729

Slade I, Bacchelli C, Davies H, Murray A, Abbaszadeh F, Hanks S, Barfoot R, Burke A, Chisholm J, Hewitt M, Jenkinson H, King D, Morland B, Pizer B, Prescott K, Saggar A, Side L, Traunecker H, Vaidya S, Ward P, Futreal PA, Vujanic G, Nicholson AG, Sebire N, Turnbull C, Priest JR, Pritchard-Jones K, Houlston R, Stiller C, Stratton MR, Douglas J, Rahman N (2011) DICER1 syndrome: clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome. J Med Genet 48(4):273–278

Tröbs RB, Krauss M, Geyer C, Tannapfel A, Körholz D, Hirsch W (2007) Surgery in infants and children with testicular and paratesticular tumours: a single centre experience over a 25-year-period. Klin Padiatr 219:146–151

Wessalowski R, Spaar HJ, Pape H, Willers R, Harms D, Göbel U (1995) Successful liver treatment of a juvenile granulosa cell tumor in a 4-year-old child by regional deep hyperthermia, systemic chemotherapy, and irradiation. Gynecol Oncol 57:417–422

Whitcomb RW, Calkins JW, Lukert BP, Kyner JL, Schimke RN (1986) Androblastomas and thyroid disease in postmenopausal sisters. Obstet Gynecol 67:89S–91S

Young RH (2005b) A brief history of the pathology of the gonads. Mod Pathol 18(Suppl 2):S3–S17

Young RH (2005c) Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. Mod Pathol 18(Suppl 2):S81–S98

Young RH, Scully RE (1985) Ovarian Sertoli-Leydig cell tumors. A clinicopathological analysis of 207 cases. Am J Surg Pathol 9:543–569

Young RH, Welch WR, Dickersin GR, Scully RE (1982) Ovarian sex cord tumor with annular tubules: review of 74 cases including 27 with Peutz-Jeghers syndrome and four with adenoma malignum of the cervix. Cancer 50: 1384–1402

Young RH, Dickersin GR, Scully RE (1984a) Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. Am J Surg Pathol 8:575–596

Young RH, Perez-Atayde AR, Scully RE (1984b) Ovarian Sertoli-Leydig cell tumor with retiform and heterologous components. Report of a case with hepatocytic differentiation and elevated serum alpha-fetoprotein. Am J Surg Pathol 8:709–718

Ovarian Adenomas, Ovarian Carcinoma, and Ovarian Small Cell Carcinoma

Benedet JL, Bender H, Jones H III, Ngan HY, Pecorelli S (2000) FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 70:209–262

Dickersin GR, Kline IW, Scully RE (1982) Small cell carcinoma of the ovary with hypercalcemia: a report of eleven cases. Cancer 49:188–197

Distelmaier F, Calaminus G, Harms D, Sträter R, Cordes U, Fleischhack G, Göbel U, Schneider DT (2006b) Ovarian small cell carcinoma of the hypercalcemic type in children and adolescents: a prognostically unfavorable but curable disease. Cancer 107(9):2298–2306

Florell SR, Bruggers CS, Matlak M, Young RH, Lowichik A (1999) Ovarian small cell carcinoma of the hypercalcemic type in a 14 month old: the youngest reported case. Med Pediatr Oncol 32:304–307

Harrison ML, Hoskins P, du Bois A, Quinn M, Rustin GJ, Ledermann JA, Baron-Hay S, Friedlander ML (2006) Small cell of the ovary, hypercalcemic type – analysis of combined experience and recommendation for management. A GCIG study. Gynecol Oncol 100:233–238

Lamovec J, Bracko M, Cerar O (1995) Familial occurrence of small-cell carcinoma of the ovary. Arch Pathol Lab Med 119:523–527

Longy M, Toulouse C, Mage P, Chauvergne J, Trojani M (1996) Familial cluster of ovarian small cell carcinoma: a new Mendelian entity? J Med Genet 33:333–335

Millar DM, Blake JM, Stringer DA, Hara H, Babiak C (1993) Prepubertal ovarian cyst formation: 5 years' experience. Obstet Gynecol 81:434–438

Pautier P, Ribrag V, Duvillard P, Rey A, Elghissassi I, Sillet-Bach I, Kerbrat P, Mayer F, Lesoin A, Brun B, Crouet H, Barats JC, Morice P, Lhomme C (2007) Results of a prospective dose-intensive regimen in 27 patients with small cell carcinoma of the ovary of the hypercalcemic type. Ann Oncol 18:1985–1989

Robertson DM, Stephenson T, Pruysers E, Burger HG, McCloud P, Tsigos A, Groome N, Mamers P, McNeilage J, Jobling T, Healy D (2002) Inhibins/activins as diagnostic markers for ovarian cancer. Mol Cell Endocrinol 191:97–103

Schneider DT, Jänig U, Calaminus G, Göbel U, Harms D (2003c) Ovarian sex cord - stromal tumors - A Clinicopathologic Study of 72 Cases from the Kiel Pediatric Tumor Registry. Virchows Arch 443:549–560

Senekjian EK, Weiser PA, Talerman A, Herbst AL (1989) Vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide in the treatment of small cell carcinoma of the ovary. Cancer 64:1183–1187

Young RH, Oliva E, Scully RE (1994) Small cell carcinoma of the ovary, hypercalcemic type. A clinicopathological analysis of 150 cases. Am J Surg Pathol 18:1102–1116

Young JL Jr, Cheng WuX, Roffers SD, Howe HL, Correa C, Weinstein R (2003) Ovarian cancer in children and young adults in the United States, 1992–1997. Cancer 97:2694–2700

Rare Tumors of the Urinary Tract

40

Filippo Spreafico and Norbert Graf

Contents

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40.1 Differential Diagnosis of Urinary Tract Tumors

Malignant renal tumors cover 6% of all childhood cancers (Pastore et al. 2006). Wilms tumor or nephroblastoma is largely the most common type of cancer in the kidney of children, accounting for more than 90% of primary renal tumors. Other tumors, like clear cell sarcoma of the kidney (CCSK), rhabdoid tumor of the kidney (RTK), renal cell carcinoma (RCC), renal medullary carcinoma, congenital mesoblastic nephroma (CMN), primitive neuroectodermal tumor of the kidney, adenoma of the kidney, oncocytoma, and others, are much rarer. As their treatment and prognosis is quite different from Wilms tumor, an early timely diagnosis is crucial to deliver the best treatment to patients.

The typical presentation of a child with a kidney tumor is a painless mass in the abdomen. Other complaints are found in <20% of children (Gutjahr et al. 1990; Graf et al. 2003). It is well known that Wilms tumor is associated with different syndromes (Scott et al. 2006). Such syndromes can guide the way to a correct diagnosis. Children with tuberous sclerosis or von Hippel–Lindau disease are at risk for developing RCC or angiomyolipoma (Sausville et al. 2009; Wiesbauer 2008). Renal medullary carcinoma, a highly malignant tumor of the epithelial origin, occurs almost exclusively in adolescents and young adults with sickle cell trait or sickle cell disease (Swartz et al. 2002). Altogether there are no typical clinical signs or symptoms in children suffering from a specific renal tumor. Furthermore, there are no specific tumor markers available.

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Imaging studies are most important, although none of these rare tumors show a specific appearance in ultrasound, CT, or MRI, comparing to nephroblastoma. Even if RTKs are more lobulated, often showing peripheral subcapsular bleedings, more lymph node involvement, and more often lung metastases, they cannot be clearly distinguished from other renal neoplasm by imaging studies alone (Schenk et al. 2004, 2005). Only in addition with further information like the knowledge of lung metastasis in a small infant having a renal mass makes the diagnosis of a specific neoplasm more likely as RTK in the above case. In all cases of a renal mass, a chest X-ray or computed tomography (CT) scan is needed for staging. Further staging procedures are mandatory in patients with specific diagnoses. In case of CCSK and RTK, an magnetic resonance imaging (MRI) of the brain should be performed as these tumors may develop brain metastasis in some patients (Smets and de Kraker 2010). Radioisotope bone scan (99 m-technetium-methylene diphosphonate) is recommended in CCSK and RCC to exclude bone metastasis (Smets and de Kraker 2010; Schenk et al. 2005).

New imaging techniques like FDG-PET and diffusion-weighted MRI (DWI) may help in distinguishing between necrotic and vital tumor areas and in the follow-up of patients in defining response to treatment (Smets and de Kraker 2010), but more research is needed to clarify their role in the diagnostic workup of rare kidney tumors in children before these techniques are routinely used in the clinical setting. Experience with new imaging methods in non-Wilms tumors of the kidney is even more limited.

A correct diagnosis can only be done by histopathology. In case of a biopsy, one should send tumor material not only for pathological analysis but also for genetics as specific genetic aberrations can be found confirming the diagnosis (Barroca 2008). For research purposes, genetic and molecular genetic analyses are mandatory and should always be initiated to find better treatments for these children.

40.2 Rare Kidney Tumors

Primary non-Wilms renal tumors represent a heterogeneous, although clinically significant, group of malignancies accounting for <1% of pediatric tumors (Pastore et al. 2006; Ahmed et al. 2007; Magnani et al. 2001). They are especially diagnosed in children aged <6 months or >12 years. The major histological groups include RCC, CCSK, and RTK. Renal primitive neuroectodermal tumor (PNET), desmoplastic small round cell tumor, anaplastic sarcoma of the kidney, and renal medullary carcinoma represent other clinically significant types of malignant tumors. The most frequent benign lesion is angiomyolipoma, while oncocytoma is extremely rare in children and adolescents (Ciftci et al. 2000). Lesions with low to borderline malignant potential are CMN, cystic nephroma (to be distinguish from a cystic appearance of a Wilms tumor), and metanephric tumors. The group of metanephric neoplasms has been recently described; basing on the extent/appearance of epithelium or stroma, they are classified into metanephric stromal tumor (pure stromal), metanephric adenoma (pure epithelial), or metanephric adenofibroma (biphasic, stromal-epithelial) (Arroyo et al. 2001). The relationship – and sometime the association – between metanephric tumors and Wilms tumor or papillary RCC has been described and warrants further study to better elucidate potential common etiopathogenesis. Other tumors, like non-Hodgkin lymphoma (mainly Burkitt) (Kumar et al. 2010) or neuroblastoma, may secondarily affect the kidney but sometimes are the only clinical disease manifestation.

Renal medullary carcinoma was originally described in 1995 and affects young adults (mean age is 20 years) of a Black ethnicity who have a sickle cell nephropathy (Davis et al. 1995). It is a rapidly growing tumor of the renal medulla, regarded as an aggressive variant of collecting duct carcinoma (Lopez-Beltran et al. 2009).

Angiomyolipoma most likely presents in children who carry a known diagnosis of the tuberous sclerosis complex. Although benign, these tumors may cause substantial morbidity if they increase in size or if cause hemorrhage. For this reason, careful imaging examination is recommended, either with computed tomography or MRI, in order to balance the proper time for surgery (conservative whenever possible) versus a wait-and-see approach.

PNET has been documented with increasing frequency in the kidney in the last decade. PNET of the kidney is clinically aggressive and requires therapeutic approach like other tumors of the Ewing sarcoma family. Noteworthy, PNET is frequently misdiagnosed as Wilms tumor, both being monotonous round cell tumors (Shet and Viswanathan 2009).

While imaging has no specific radiological features that can reliably distinguish between the histological

types of renal tumors (Miniati et al. 2008), one of the most useful criterion for suspecting among the types of tumor is the age of the children. More than 50% of children with RCC are diagnosed after the age of 15 years, whereas >80% of patients with CCSK and RTK are younger than 4 years at diagnosis (Ries et al. 2008; Zhuge et al. 2010). CMN is the primary diagnostic consideration for a renal mass in the neonate, and its incidence decreases quickly with advancing age (van den Heuvel-Eibrink et al. 2008). RTK represents the primary diagnostic consideration for a metastatic renal tumor in children <7 months of age.

Non-Wilms tumors tend to affect more boys under the age of 5 years while more girls above the age of 15 years (Zhuge et al. 2010).

Consistent with their rarity, there is a paucity of published reports of these tumors. The rarity of the different types of primary non-Wilms renal tumors and the importance of prescribing the correct type-specific adjuvant therapy – if any – render central pathology review fundamental for the correct and modern clinical assessment of pediatric renal tumors (Vujanic et al. 2009). A recent analysis of the SEER registry pointed out that patients diagnosed with a non-Wilms tumor after 1989 had much improved survival compared with those diagnosed prior to 1989, likely reflecting improvement in the diagnosis and/or treatment (Zhuge et al. 2010). Entering homogeneous groups of tumors into centralized histological database facilitates the description and classification of new entities.

Molecular biology studies have helped us in recognizing that some renal tumors are identical to tumors of other sites (such as cellular mesoblastic nephroma and infantile fibrosarcoma of soft tissue, renal and extra-renal rhabdoid tumor) as well as that some tumors of other sites may also occur in the kidney (PNET, desmoplastic small round cell tumor, synovial sarcoma). These molecular new findings are helping researchers to move from a "kidney-oriented" classification to a classification system whose fulcrum is the tissue origin of the tumor more than the fact that they are in the kidney (Fig. 40.1).

40.3 Renal Cell Carcinoma (RCC)

RCC is rare in the first two decades of life and accounts for approximately 5% of pediatric renal tumors (Selle et al. 2006; Pastore et al. 2006; Silberstein et al. 2009; Argani and Ladanyi 2003). The big discovery in recent years regarding pediatric RCC has been the characterization of the translocation RCCs (Argani et al. 2003; Argani and Ladanyi 2005, 2006). Translocations most frequently involve the TFE3 gene on chromosome Xp11.2 or, less commonly, the TFEB gene on chromosome 6p21. It is likely that a large proportion of RCC in children, approximately one-third to two-thirds, belong to the translocation RCC (Argani and Ladanyi 2005, 2006; Sausville et al. 2009).

While much information is now available as far as the complementary treatment for RCC in adults, studies on children dealt with retrospective case reports, or mono- and pauci-institute series (Baek et al. 2010; Estrada et al. 2005; Geller and Dome 2004; Geller et al. 2008; Indolfi et al. 2003; Ramphal et al. 2006; Selle et al. 2006; Wu et al. 2008; Rao et al. 2009). The potential bias inherent in non-consecutive case series and reports prevents a definitive formulation of standard therapeutic guidelines for RCC in children and adolescents.

Radical nephrectomy is most important for therapy, while the role of extensive lymph node (LN) dissection – in the absence of LN spread– and of partial nephrectomy till remain clue issues for children as well.

Overall survival rates for childhood RCC are around 50–60%, with outcomes worsening with advancing stages (Indolfi et al. 2003; Carcao et al. 1998; Geller and Dome 2004; Ahmed et al. 2007; Silberstein et al. 2009; Selle et al. 2006). Patients with tumor localized in the kidney with or without regional LN spread have a good prognosis, while outcome remains dismal for patients with distant hematogenous metastases. In the extensive review by Geller and Dome, stage-adapted survival rates for pediatric RCC were 92.5%, 84.6%, 72.7%, and 12.7% for modified Robson stages I to IV, respectively (Geller and Dome 2004). Children with LN+M0 RCCs are likely to have an intermediate prognosis, with survival rate around 50–70% (Geller and Dome 2004; Geller et al. 2008; Indolfi et al. 2003; Selle et al. 2006).

40.3.1 Epidemiology

The overall annual age-adjusted incidence is 0.01/100,000 children. Median age at diagnosis is 9–12 years, with equal prevalence in boys and girls

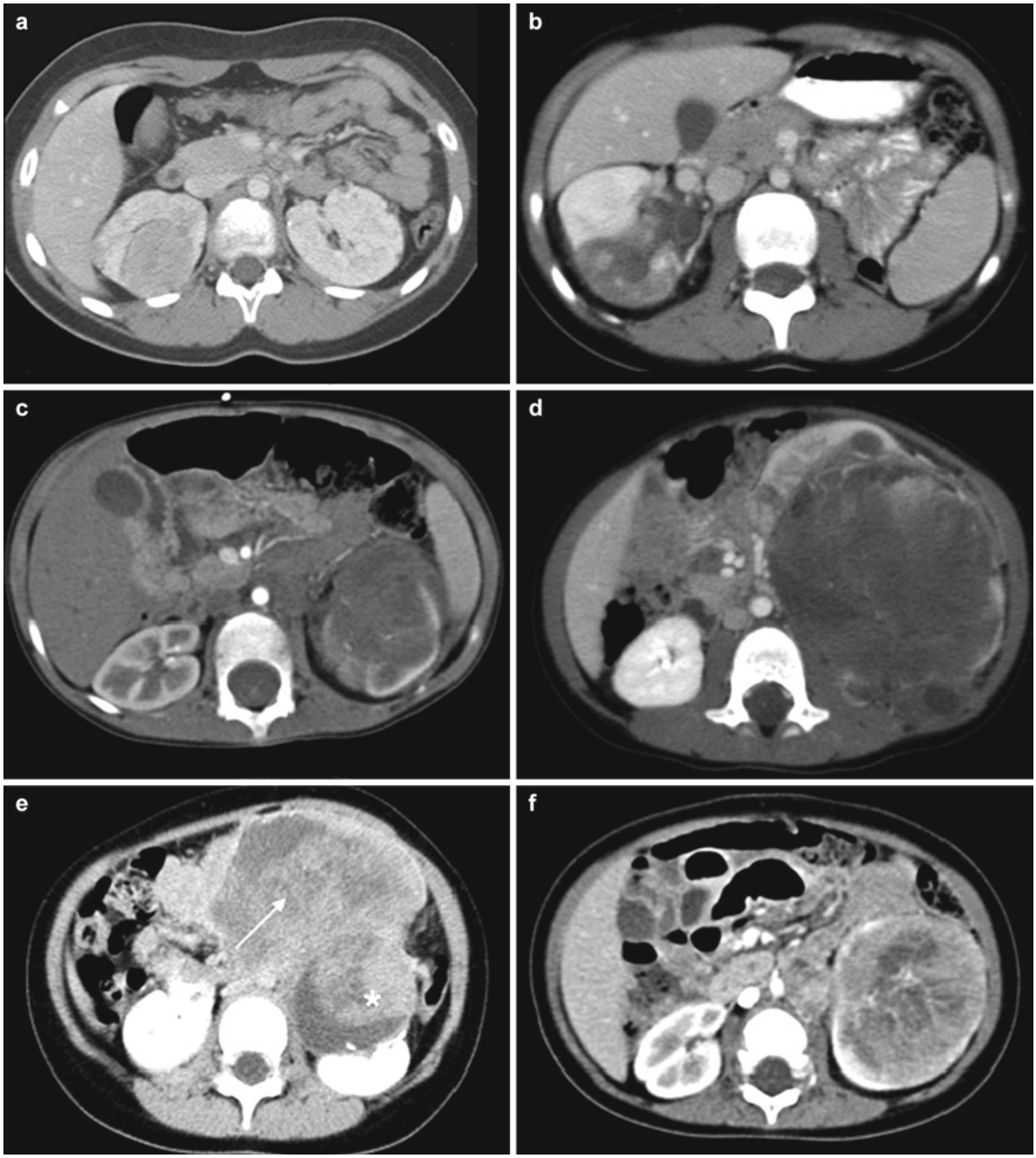

Fig. 40.1 Post-contrast CT imaging of: (**a**) angiomyolipoma (male, 13 year-old); (**b**) primitive neuroectodermal tumor (female, 15 year-old); (**c**) Wilms tumor (male, 4 year-old); (**d**) clear cell sarcoma (male, 3 year-old); (**e**) 6-year-old female who displayed two rather distinct nodules, that at microscopic examination turned out to be MiTF+RCC (*) and concomitant Wilms tumor (*arrow*); (**f**) Xp11.2 translocation carcinoma (female, 9-month-old)

(Geller and Dome 2004; Selle et al. 2006; Pastore et al. 2006; Silberstein et al. 2009; Indolfi et al. 2003; Ramphal et al. 2006). Despite RCC mostly occurs as a primitive renal tumor, it has been also recognized as a second neoplasm arising in children treated with chemotherapy (Schafernak et al. 2007; Argani et al. 2006). The association between RCC and neuroblastoma has been specifically described as a unique one, so that

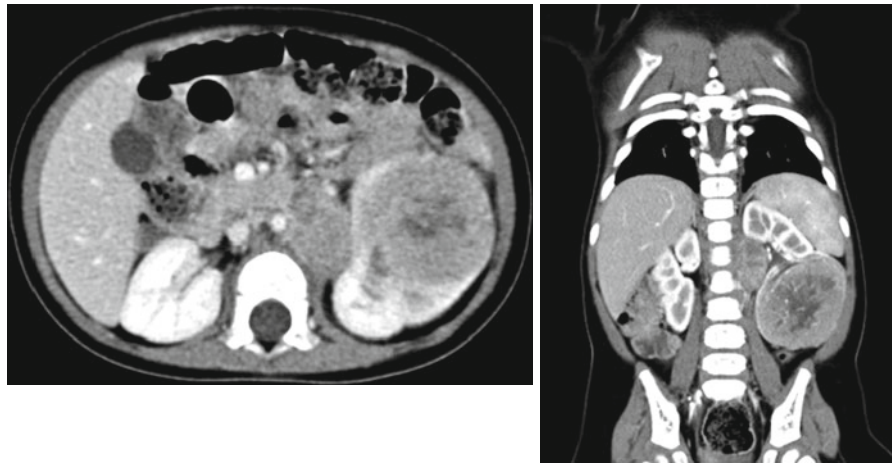

Fig. 40.2 Post-contrast CT scan of a Xp11.2 translocation carcinoma in a 9-month old baby girl

post-neuroblastoma RCC has been included in the 2004 WHO renal tumor classification as a distinct new category (Eble et al. 2004).

The strong association with the von Hippel–Lindau gene, known for adults (Rini et al. 2009), rarely occurs in children.

40.3.2 Diagnosis

Children with RCC may present with local or systemic symptoms, although current prevalent use of ultrasound and cross-sectional imaging is associated with an increasing incidental detection of asymptomatic small renal tumors (Estrada et al. 2005; Cook et al. 2006; Gill et al. 2010). Local signs and symptoms include gross hematuria, flank pain, or a palpable abdominal mass. Rarely children present with the full above mentioned clinical triad (Indolfi et al. 2003; Geller and Dome 2004). Systemic symptoms may be due to metastases or paraneoplastic syndromes, such as hypercalcemia, fever, or hypertension, which are rarely diagnosed in children.

A 30% rate of metastatic disease has been reported in the pediatric population (Geller and Dome 2004; Silberstein et al. 2009). About 5–10% of adult RCCs extend into the venous vessels as tumor thrombi, often ascending the inferior cava vein (Rini et al. 2009), and this situation, which has important surgical implications, can be encountered in children as well despite no incidence estimation.

Similar to adults, tumor stage in pediatric RCC represents a good prognostic indicator. The TNM system is the more frequently adopted, while stage designation according to modified Robson system (Carcao et al. 1998) is rarely encountered. Geller and Dome reported stage-specific incidence as follows: 43.2% low-stage tumors (stage I and II) and 56.8% high-stage tumors (stage III and IV). Such advanced presentation is probably reflective of LN+M0 status (modified Robson stage IIIb; TNM stage III or IV) (Geller and Dome 2004) (Fig. 40.2).

40.3.3 Pathology and Classification

Overall, the clear-cell type of RCC, predominant in adults, is much less frequent in children, where in turn the papillary forms are much more frequent (Bruder et al. 2004; Argani and Ladanyi 2003; Sebire and Vujanic 2009).

A large part of RCCs in children and young adults show peculiar morphology, immunophenotype and genetic alterations, and belong to the group of translocation RCCs (Argani and Ladanyi 2003, 2005; Camparo et al. 2008). It is realistic to presume that many RCCs reported as papillary or clear cell in previous pediatric series would turn on contemporary examination to be translocation RCCs.

40.3.4 TFE3/MiTF Translocation RCCs

Translocations involving the TFE3 gene at Xp11.2 with varying partners (Argani and Ladanyi 2005) or the TFEB gene (at 6p21) in the translocation t(6;11)(q21;q13) (Argani et al. 2001b) characterize these

tumors. Fusion targets for TFE3 include PRCC in 1q21 (Argani et al. 2007), ASPL of alveolar soft part sarcoma in 17q25 (Argani et al. 2001a; Argani et al. 2007), PSF in 1p34 (Argani et al. 2005), and CLTC in 17q23 (Argani et al. 2003). TFE3 and TFEB are members of the microphthalmia transcription factor (MiTF) family (a subfamily of basic helix-loop-helix-leucine zipper transcription factors), together with MiTF and TFEC.

Many of these tumors show a high-grade (Fuhrman grade 3), type 2 papillary morphology and are made up by voluminous, large oxyphilic cells (Argani and Ladanyi 2005; Camparo et al. 2008; Ramphal et al. 2006). Cases with a solid, alveolar, nested, paraganglioma-like, or tubulo-papillary pattern are reported as well. The immunophenotype is distinct and quite different from the adult-type RCCs. There is a variable, usually very low or even absent expression of epithelial markers, i.e., keratins 8, 18 (CAM5.2); keratin 7; and EMA. CD10 and racemase are usually expressed. Some cases express melanocytic markers, i.e., HMB-45 and Melan-A. In addition, there is nuclear reactivity for TFE3 or TFEB.

40.3.5 Principles of Treatment

The emerging differences between childhood and adulthood RCC probably prevent a direct application and translation of therapies that have been validated for adults to children.

Because RCC is among the most resistant of tumors to systemic therapy and radiotherapy, the cornerstone of therapy for RCC in children remains radical nephrectomy. Since nephron-sparing approaches that preserve healthy renal parenchyma are advocated for adults and demonstrated good long-term oncologic outcome (Ficarra 2007; Touijer et al. 2010), it is reasonable that they will be evaluated in children and adolescents as well (Cook et al. 2006), at least in cases very carefully selected by experienced surgeons.

Question as to what is the more adequate extension of retroperitoneal LN dissection remains relatively unanswered. To our knowledge, no formal guidelines currently exist regarding the extent of LN dissection in adults as well (Margulis and Wood 2008; Blom et al. 2008). Nevertheless, while in adults lymphatic spread by RCC, and mostly by clear-cell RCC, certainly decreases outcome, it is likely not the same for children (Geller and Dome 2004; Geller et al. 2008; Selle et al. 2006; Renshaw 2005). From the available experiences, children with clinical evidence of regional LN metastases derive therapeutic benefit from involved LN dissection. It remains less clear, but worth to be analyzed thoroughly, whether children with clinically normal LNs can be targeted for lymphadenectomy as an adjunct to radical nephrectomy. Patients with unsuspected LN spread, in whom LNs randomly sampled turn out to be metastatic at microscopic examination, raise the dilemma of second-look lymphadenectomy.

Overall, chemotherapy has little to no role in the treatment of RCC (Escudier 2010a, b), pending new insights on similarities between childhood RCC and alveolar soft part sarcoma, in which some chemotherapy agents may be effective (such as doxorubicin). Despite no result data have been published so far; it is worth to be mentioned that pediatric oncologists have used doxorubicin, gemcitabin, oxaliplatin, and irinotecan as isolated experience, with anecdotal responses in translocation RCCs.

Until 2005, only high-dose interleukin-2 (IL-2) had been approved by the Food and Drug Administration for the treatment of RCC in adults, and this approval was based on durable complete responses obtained in only 7–8% of patients with metastatic RCC. The landscape of systemic therapies in RCC has been recently changed by the introduction of drugs designed to target tumor-related angiogenesis and signal transduction (Sun et al. 2010; Brugarolas 2007). These are the multitargeted receptor tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib), the inhibitors of the mTOR pathway (temsirolimus, everolimus), and the anti-angiogenic monoclonal antibody bevacizumab.

When used as first- and second-line therapies for metastatic RCC, these novel agents have demonstrated previously unprecedented response rates and improvements in time to progression in phase III trials (Escudier et al. 2007a, b, 2009, 2010; Motzer et al. 2007, 2009; Hudes et al. 2007; Bellmunt and Guix 2009; Soulières 2009; Bukowski 2010). On the other hand, the utility of these therapies in the adjuvant setting remains unproven. This uncertain benefit, together with their toxicity and the relatively better outlook for children and adolescents with completely resected LN+M0 RCC, support not currently using adjuvant therapies in such pediatric RCCs (Escudier and Kataja 2010).

Despite these several targeted therapies available for RCC, each with different profile of risk versus benefit, at the time of this writing, no data have been published for pediatric age.

Many of the pediatric RCC series covered a very long time span – institutional and population-based reports may need as long as 20–40 years to accrue a significant number of children with this uncommon tumor – and mostly discussed results obtained prior to the recently introduced targeted therapies (Geller and Dome 2004; Indolfi et al. 2003; Baek et al. 2010). Currently, the role of targeted agents such as tyrosine kinase inhibitors should be reserved to children with unresectable metastatic or advanced-stage RCC. What might be recommended for metastatic pediatric RCCs is to adopt sequential treatment with VEGF pathway-targeted therapies, optimizing efficacy and safety results.

A further element which complicates the potential translation of therapeutic findings from adult to pediatric RCC relays in that a major proportion of RCCs included in adult clinical trials are clear-cell RCCs. On the other hand, the optimal therapy for the Xp11.2 translocation RCCs remains to be proven, but case report describing significant response to anti-angiogenics have been described (Joshi and Banerjee 2008; Malouf et al. 2010).

40.4 Rhabdoid Tumor of the Kidney (RTK)

Rhabdoid tumors of the kidney (RTKs) are rare and extremely aggressive malignancies that generally occur in infants and young children. These tumors tend to develop early metastasis. Their prognosis remains dismal despite aggressive treatments. The first description is done by Haas et al. in 1981 (Haas et al. 1981). Despite a multitude of case series and single reports, very little is known about this tumor and done in prospective national or international clinical trials (Athale et al. 2009; Corey et al. 1991; Gururangan et al. 1993; Hirose et al. 1996). Common therapeutic regimens do use intensive anthracycline-based polychemotherapy regimens and aggressive local therapy (Chi et al. 2008; Squire et al. 2007; Wagner et al. 2002; Waldron et al. 1999; Zimmerman et al. 2005). Recent publications describe successful therapeutic approaches even in primarily metastasized or relapsed disease (Chi et al. 2008; Zimmerman et al. 2005).

40.4.1 Molecular Genetics

Common to rhabdoid tumors of any anatomical site (central nervous system, kidney, other soft tissues) are alterations in chromosome 22. Loss of genetic material from chromosome 22q11 in rhabdoid tumors has been demonstrated by molecular genetic analyses, fluorescence in situ hybridization, and loss of heterozygosity studies (Biegel et al. 1996; Rickert and Paulus 2004). The tumor suppressor gene SMARCB1 (hSNF5/INI1) resides on the long arm of chromosome 22. Versteege et al. isolated the gene SMARCB1 (hSNF5/INI1) from chromosome 22q11.2. SMARCB1 is a member of the SWI/SNF complex (Versteege et al. 1998). The gene contributes to gene transcription through chromatin remodeling (Zhang et al. 2002). Transgenic mice heterozygous for SMARCB1 develop rhabdoid tumors and T-cell lymphomas (Roberts et al. 2000, 2002). SMARCB1 mutations have been detected in all nine exons (Biegel et al. 2002b) and show a broad mutational spectrum across tumors from different anatomical sites (Kordes et al. 2010). Today mutations can be detected at least in about 80% of cases on chromosome 22q11.2 (Biegel et al. 2002a; Jackson et al. 2009; Versteege et al. 1998). An additional 20–25% of tumors have reduced expression at the RNA or protein level, indicative of a loss-of-function event. It is unclear if this mutation indicates a common histogenesis of rhabdoid tumors (Parham et al. 1994; Weeks et al. 1989; Wick et al. 1995).

Germline mutations in SMARCB1 do occur, and families are reported with more than one affected member, as well as patients with synchronous rhabdoid tumors of the CNS and the kidney (Proust et al. 1999; Sevenet et al. 1999; Taylor et al. 2000). Familial cases are summarized under the term "rhabdoid tumor predisposition syndrome" – RTPS (Kordes et al. 2010; Louis et al. 2007). While the majority of the patients affected by the rhabdoid tumor predisposition syndrome are characterized by SMARCB1 mutations, one report describes a family with two affected children without mutation of SMARCB1 (Frühwald et al. 2006). Furthermore, there are family members described who carried a germline mutation and who did not develop any tumor (Ammerlaan et al. 2007; Janson et al. 2006). Nevertheless, genetic counseling appears mandatory in families with RTPS. In case of a mutation in SMARCB1 within the tumor, analysis of constitutional DNA from the blood of the patient needs to be done. If a germline mutation is detected, parents have to be informed about the potential risk in siblings of the affected patient (Fig. 40.3).

A correlation between the mutational status of certain nucleotides and the clinical course of the disease has not been demonstrated. However, reports from the

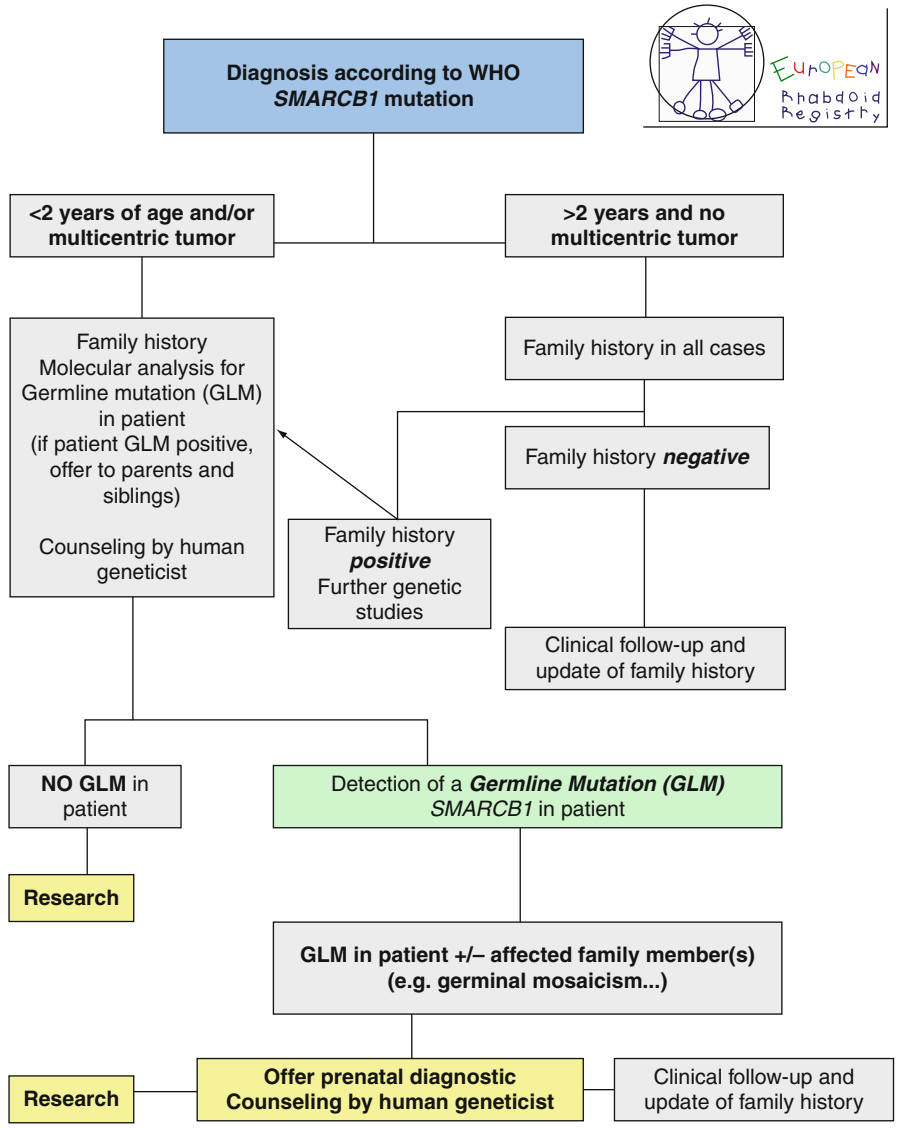

Fig. 40.3 Flow chart for genetic counseling of patients with suspected rhabdoid tumor predisposition (From: Frühwald, M European Rhabdoid Registry protocol 2010)

literature suggest that patients with germline mutations are younger and are characterized by an almost inevitably fatal course (Kordes et al. 2010).

40.4.2 Diagnosis

RTKs constitute 2% of all kidney tumors in infants and children. Fever and hematuria in a young patient (mean age 11 months) with a high tumor stage should suggest the diagnosis of RTK. Tumor staging system is the same as in nephroblastoma but with a higher incidence of metastatic disease even in young infants. Among 639 cases of kidney tumors in the first 7 months of life with specified histology and stage, 9/11 stage IV tumors were RTKs, as reported by van den Heuvel-Eibrink et al. (2008). RTK tends to metastasize to the lungs and the brain. Up to 15% of patients with RTK also have brain lesions. Because of the coincidence with brain metastasis, a cerebral MRI is always indicated.

The diagnosis of RTK can only be done by histology. Today the diagnosis of RTK needs to be confirmed by immunohistochemical and/or molecular genetic

techniques showing the loss of INI1 protein expression resulting from SMARCB1 mutations (Judkins 2007). In every case, tumor material should be stored for research to perform gene array and other experiments for gaining further knowledge (Huang et al. 2006).

40.4.3 Histopathology

Histopathologically, RTKs are characterized by cells with an eccentric nucleus and prominent nucleolus, abundant cytoplasm with eosinophilic inclusion bodies and distinct cellular membranes, somewhat resembling the rhabdomyoblastic differentiation of rhabdomyosarcomas (Sotelo-Avila et al. 1986). Rhabdoid differentiation may also be seen in a variety of other entities such as meningioma, melanoma, and lymphoma. Rhabdoid cells are characterized by expression of vimentin, EMA (epithelial membrane antigen), and cytokeratins, less commonly by SMA (smooth muscle actin) (Louis et al. 2007; Jackson et al. 2009; Tomlinson et al. 2005). The loss of INI1 protein confirms the diagnosis of rhabdoid tumors.

40.4.4 Treatment and Prognosis of RTK

Between 1984 and 1999, 70 children with rhabdoid tumors of any anatomical site were diagnosed in Germany. 35 children were below 1 year of age, 10 between 1 and 2 years, and 9 between 2 and 3 years. Only 10 children were older than 4 years. 32 tumors were localized in the kidneys, 25 in soft tissue (MRT), and 13 in the CNS (AT/RT). 20% of AT/RT and 40% of RTK patients demonstrated metastases at diagnosis. Treatment was according to the respective available protocols at that time (HIT, SIOP, CWS). Twenty-eight patients received radiotherapy (at a dose ranging between 30 and 40 Gy) in addition to surgery and chemotherapy. Of the 70 registered patients, 46 died within 2 years of diagnosis. Two additional patients succumbed to the disease until the fourth year after diagnosis. More follow-up data are currently not available. The prognosis was dismal regardless of site of the primary tumor or the protocol used. The only statistically relevant negative prognostic factor was metastatic disease (Fig 40.4) (Reinhard et al. 2008).

In the United Kingdom, patients with RTK have been treated according to the Wilms tumor studies

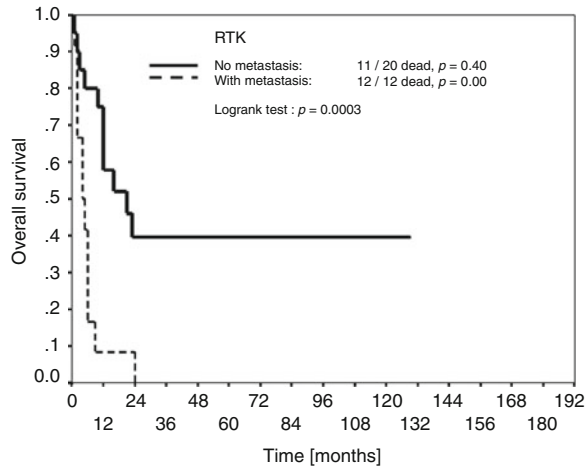

Fig.. 40.4 Outcome of RTK treated according to SIOP protocols in Germany

UKW2 and UKW3, containing a combination of vincristine, actinomycin-D, and doxorubicin (Grundy et al. 2004; Mitchell et al. 2006). The survival rate of 21 patients was 35% (SD ± 9%). All deaths occurred within 13 months following diagnosis. Two stage I patients survived; three patients with stage III died. Four of nine patients with stage III survived. Of seven patients with stage IV disease, there was only one survivor. Two of the stage III patients received radiotherapy.

In the United States, patients with RTK were enrolled into the National Wilms Tumor Studies (NWTS) studies until recently. These studies employed a drug regimen with vincristine, actinomycin-D, and doxorubicin with or without cyclophosphamide (D'Angio et al. 1989; Tomlinson et al. 2005). Despite high therapy intensity, the survival rate remained unsatisfactory with 4-year overall survival (OS) for stage I patients of 33%, stage II of 47%, stage III of 22%, and stage IV of 8% (Tomlinson et al. 2005). Similar results have been reported by the International Society of Paediatric Oncology (Vujanic et al. 1996) and the United Kingdom group (Grundy et al. 2004). To improve these results, the National Wilms Tumor Study-5 (COG-Q9401) enhanced treatment by using carboplatinum and etoposide with cyclophosphamide (regimen RTK). This trial arm was preliminary closed because of poor outcome (26% survival rate). In a review of 142 patients from NWTS-1 through NWTS-5, stage and age were significant prognostic factors. Patients with stage I and stage II disease had an OS rate

of 42%; higher stage was associated with a 16% OS. Infants younger than 6 months at diagnosis demonstrated a 4-year OS of 9%, whereas OS in patients aged 2 years and older was 41%. All except one patient with a central nervous system lesion died (Tomlinson et al. 2005). Based on the currently available data, the role of radiotherapy in the treatment of RTK cannot be judged conclusively (Tomlinson et al. 2005). A recent window study using irinotecan in the induction was prematurely closed due to ineffectiveness (COG AREN0321).

40.4.5 European Rhabdoid Registry (EU-RHAB)

As prognosis of children with rhabdoid tumors is dismal, new diagnostic and therapeutic strategies are demanding. In Europe a European Rhaboid Registry (EU-RHAB) has been launched as a registry for all rhabdoid tumors regardless of site. The EU-RHAB hopefully will build the basis for future therapeutic trials by contributing to improvements in the diagnostic and eventually therapeutic management of affected patients. The EU-RHAB contains treatment recommendations, which were generated from data derived from the current literature and the investigators' clinical experience, other than from the GPOH and SIOP studies for high-risk renal tumors, soft tissue sarcomas, and pediatric brain tumors. The EU-RHAB aims at giving a standardized therapeutic approach. A patient with RTK should be referred to a center for pediatric oncology and enrolled in a prospective trial or registry. Treatment planning by a multidisciplinary team of cancer specialists (pediatric surgeon or pediatric urologist, pediatric radiation oncologist, and pediatric oncologist) with experience treating renal tumors is required to determine and implement optimum treatment.

40.5 Clear Cell Sarcoma of the Kidney (CCSK)

CCSK is an important primary renal tumor representing one of the most common unfavorable kidney tumors in childhood (Argani et al. 2000). CCSK was initially recognized as a distinct clinicopathologic entity with a high propensity to metastasize to bone (Kidd 1970). Marsden and Lawler noted osseous metastases in 60% of patients with CCSK and coined the term "bone-metastasizing renal tumor" (Marsden and Lawler 1980). In addition to pulmonary and bone metastases, CCSK may also spread to brain and soft tissue. CCSK is associated with a significantly higher rate of relapse, even late relapse (Kusumakumary et al. 1997) and death than Wilms tumor. The prognosis for CCSK improved after the introduction of anthracyclines to modern treatment regimens, with survival rates approaching 90% for non-metastatic tumors (authors' unpublished data).

40.5.1 Molecular Genetics

Cytogenetic studies of CCSK have reported balanced translocations t(10;17)(q22;p13), t(10;17)(q11;p12), and del(14)(q24.1q31.1). Although the tumor suppressor gene p53 is located at the chromosome 17p13 breakpoint, p53 abnormalities are rarely present in these tumors. The t(10;17) breakpoint and deletion of chromosome 14q24 suggest that other genes are involved in tumor pathogenesis (Brownlee et al. 2007).

Comparative genomic hybridization analysis done by Schuster et al. revealed quantitative abnormalities in only 4 of 30 CCSKs. Two of them showed gain of 1q, one showed loss of 10q, and the other showed loss of terminal 4p. The remaining two cases demonstrated chromosome 19 loss and chromosome 19p gain, respectively. All 22 cases in their series informative for 11p15 showed retention of both alleles. Of 14 CCSKs informative for IGF2, 6 showed biallelic expression (Schuster et al. 2003). The high frequency of LOI for IGF2 in CCSKs (43%) is comparable to that reported in Wilms tumors. This suggests that IGF2, a potent growth factor, may play a role in the development or progression of CCSK (Schuster et al. 2003).

Cutcliff et al. found in gene expression profiles of CCSK differentially expressed genes which they grouped into four categories: (a) a wide variety of neural markers, (b) members of the Sonic hedgehog pathway, (c) members of the phosphoinositide 3-kinase/Akt cell proliferation pathway, and (d) known therapeutic targets. In particular, they found that CD 117 – an epidermal growth factor receptor – is upregulated at the protein level in many CCSKs, providing potential therapeutic targets. In addition, they claimed that nerve growth factor receptor represents a promising diagnostic tool for CCSK (Cutcliffe et al. 2005). Huang et al.

could show that the most common malignant tumors arising in the kidney have distinct and different gene expression profiles despite their frequent histologic similarities, helping to provide much greater diagnostic confidence than only routine pathologic examination. The top eight upregulated genes they did find in CCSK are: forkhead box F1 (FOXF1), tumor suppressor homeobox HB9 (HLXB9), DNA segment chromosome 4 (D4S234E), neuronal pentraxin I (NPTX1), forkhead box F2 (FOXF2), protocadherin 11 X-linked (PCDH11), engrailed homolog 2 (EN2), and neuronal pentraxin receptor (NPTXR) (Huang et al. 2006).

Correlations between gene mutations and outcome are not described yet. p53 abnormalities are controversially discussed (Argani et al. 2000; Brownlee et al. 2007).

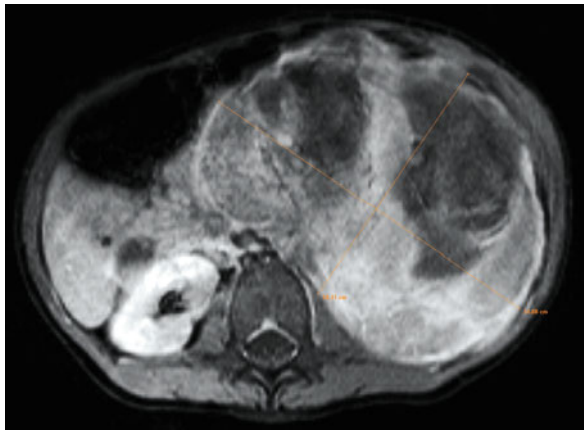

Fig. 40.5 MRI at the time of diagnosis in a 9-year-old girl with CCSK. Tumor volume at the time of diagnosis: 1,370 mL with no regression after 4 weeks of preoperative chemotherapy according to the SIOP Wilms tumor protocol with vincristine and actinomycin-D

40.5.2 Diagnosis

CCSK constitutes about 4% of all kidney tumors in children. There is no distinct clinical presentation to differentiate it from nephroblastoma. Tumor staging is the same as in nephroblastoma. Only 2% of kidney tumors in the first 7 months of life are CCSKs (van den Heuvel-Eibrink et al. 2008). In a series of 50 patients from GPOH, the median age at diagnosis was 2.4 years, ranging from 2 months to 19.2 years with an excess of boys (male to female 1.6:1) (Graf N 2010). This is in accordance with the findings of Argani et al. who found a male to female ratio of 2:1 and a mean age of 36 months in a series of 351 cases (Argani et al. 2000). Staging procedures have to be done as for nephroblastoma, with the addition of a bone scan and an MRI to the brain, as CCSKs do metastasize to the bone, lungs, and the brain. Imaging studies cannot differentiate between nephroblastoma, CCSK, and other renal tumors (Figs. 40.3 and 40.5)

40.5.3 Histopathology

The classic pattern of CCSK is defined by nests or cords of cells separated by regularly spaced fibrovascular septa (Argani et al. 2000). Typical gross features included large size, a mucoid texture, foci of necrosis, and prominent cyst formation. Nine major histologic patterns were identified (classic, myxoid, sclerosing, cellular, epithelioid, palisading, spindle, storiform, and anaplastic) (Argani et al. 2000). Only vimentin is consistently immunoreactive in immunohistochemical stains. Consistently, negative results with other antibodies help to exclude other tumors. The p53 gene product is rarely overexpressed in non-anaplastic CCSKs but strikingly overexpressed in anaplastic CCSKs (Argani et al. 2000).

40.5.4 Treatment and Prognosis of CCSK

After the introduction of anthracyclines to the treatment protocol, the prognosis of CCSK has changed. Previously, relapses have occurred in long intervals after the completion of chemotherapy (up to 10 years); however, with current therapy, relapses after 3 years are uncommon (Seibel et al. 2004). Overall survival is in the range of 70% today (Argani et al. 2000). A multivariate analysis done by Argani et al., including 182 patients from NWTSG trials 1–4 revealed four independent prognostic factors for survival: treatment with doxorubicin, stage, age at diagnosis, and tumor necrosis (Argani et al. 2000).

Over a period of 7 years, 50 patients were treated according to the SIOP 93-01/GPOH trial (Graf N 2010). Only three patients had metastatic disease at the time of diagnosis (all with multiple bone metastasis, one patient also with lung metastasis). Forty-one patients did receive preoperative chemotherapy

with vincristine and actinomycin-D for 4 weeks and, in addition, doxorubicin in case of metastatic disease for 6 weeks. Local stage after surgery was stage I: 27, stage II: 9, and stage III: 14. In 24 patients local histology was changed by reference histology, in 16 cases from a different histology to CCSK, and in 8 cases from CCSK to another histology. Most often, blastemal predominant Wilms tumor and RTK were misdiagnosed. None of the metastatic patients was in CR after preoperative chemotherapy. Postoperative high-risk chemotherapy with four drugs (carboplatin, etoposide, ifosfamide, and doxorubicin) was given to all patients for 34 weeks. Patients did receive postoperative local irradiation in stage II and III of 25.2 Gy and a boost in case of macroscopic remaining tumor or positive lymph nodes of 10.8 Gy. The 5-year event-free survival is 85% with a 5-year overall survival of 91% for this group of patients with a median follow-up of 68.4 months. Only five patients died, four because of tumor progression and one patient because of a cardiomyopathy. A multivariate analysis showed only a significant influence of stage III on event-free survival. No influence was found for age. As all patients did receive doxorubicin the influence of this drug to outcome could not be analyzed. This excellent result is also important as it shows that preoperative chemotherapy with only vincristine and actinomycin-D did not negatively influence the outcome. Two of the three patients with stage IV are in first CR for 4.5 and 5 years. Their treatment was intensified by high-dose chemotherapy with autologous stem cell transplantation in first line. The third patient with metastatic disease died of congestive heart failure due to doxorubicin and irradiation to the lungs and ribs.

Most remarkable is the relapse pattern. Out of seven relapses, six did occur in the brain. Two of them could be rescued with surgery, irradiation, and second-line therapy. They are in second complete remission for 7.4 and 8.8 years (Graf N 2010). Such a relapse pattern in the brain is also reported by other groups (Seibel et al. 2006; Radulescu et al. 2008), underlining that the brain is a frequent site of recurrent disease in CCSK.

As prognosis of patients with CCSK is excellent today, if they receive adequate therapy, all patients with this tumor have to be referred to a center of pediatric oncology.

40.6 Differential Diagnosis and Treatment of Urothelial and Bladder Tumors

Pediatric tumors of the lower urinary tract are extremely rare and comprise dissimilar histological subtypes. Bladder tumors are usually of mesodermal origin in children <10 years, and tumor of the epithelial origin are extremely rare, above all below the age of 10 years (Alanee and Shukla 2009).

Macroscopic hematuria and symptoms of urinary tract infections often represent the initial presentation (Patel et al. 2008; Lerena et al. 2010; Fine et al. 2005). Boys are generally more affected than girls regardless of the histology (2–3:1).

The rarity of bladder tumors in children makes it very difficult to estimate their incidence and survival. A recent paper from the Surveillance, Epidemiology, and End Results (SEER) database focused on the incidence of pediatric bladder tumors. Among 140 identified cases of bladder neoplasms in children aged <18 years (over the past 30 years), papillary urothelial neoplasm of low malignant potential (PUNLMP) and embryonal rhabdomyosarcoma comprised 50.7% and 36.4% of the tumors, and transitional cell carcinoma (TCC) accounted for 9.3% (Alanee and Shukla 2009). Noteworthy, the incidence of a given histological subtype was related to the age at presentation. Embryonal rhabdomyosarcoma was the predominant type in children aged <12 years, being TCC extremely rare. It was around puberty when TCC was more common and overcame the other subtypes. The incidence of pediatric bladder tumors significantly increased over the period of the study; however, the authors warn that this can be due to the improved reporting to the SEER database more than to an actual increase. Survival calculated at 1 and 2 years after initial diagnosis was 93.6% and 97.5%.

Mesenchymal bladder tumors may exceptionally include, other than rhabdomyosarcoma, leiomyosarcoma, inflammatory myofibroblastic tumor (Berger et al. 2007; Houben et al. 2007), hemangioma (Wiygul and Palmer 2010), lymphangioma (Niu et al. 2010), and pheochromocytoma (Mou et al. 2008).

TCC of the bladder has a high incidence in adults, but it is uncommon in children and adolescents, and only small case series have been described in children (Patel et al. 2008; Lerena et al. 2010; Yossepowitch and Dalbagni 2002). Apart from the SEER report,

currently, there are about 125 cases of patients <20 years of age reported in the literature, with only 20 of them in patients <10 years of age (reviewed in Lerena et al. 2010). Despite some genetic conditions seem to increase the risk of TCC of the bladder in adults, such as Cowden disease, hereditary nonpolyposis colon cancer, familial increased risk, none of these have been reported to be related to this cancer in children (Giedl et al. 2006). Adolescents and young adults with Costello syndrome are at higher risk of TCC of the bladder (Gripp and Lin 2005). A known past history of smoking in adolescents has been advocated as a possible risk factor. Hematuria is the most common symptom of presentation. This finding emphasizes the need to exclude urothelial tumors in all young patients who present with painless hematuria (Hoenig et al. 1996), even though gross hematuria in children most often has a benign cause. Urine cytology has a good sensitivity and specificity only in high-grade tumors, and since the great majority of TCC in children are well differentiated, urine cytology is not recommended for diagnosis and or follow-up in children.

Fine et al. reported on a relatively large series of patients younger than 20 years with urothelial neoplasms, diagnosed following modern clinicopathological classification (Fine et al. 2005; Eble et al. 2004). This analysis revealed and confirmed that these tumors are more common in males, are likely to manifest as hematuria, occur as solitary lesions, and are generally of low-grade histology. These neoplasms have low recurrence potential, with extremely favorable prognosis. Cystoscopically, the majority of the lesions were described as papillary. Lesions ranged between urothelial papilloma (2 cases), PUNLMP (10 cases), noninvasive low-grade papillary urothelial cancer (8 cases), and noninvasive high-grade papillary urothelial cancer (3 cases).

Definitive diagnosis for pediatric tumors of the lower urinary tract is usually performed by cystoscopy, which also allows evaluation of tumor extensions, excision, or biopsy. Ultrasound is an excellent initial diagnostic tool for bladder tumor in children. Transurethral resection represents the treatment of choice for papillary urothelial neoplasms. Interval cystoscopy has been advocated as the best method to follow these patients; however, while only cystoscopy allows for histological diagnosis, the need for general anesthesia and the risk of urethral manipulation make its limited use preferable, with ultrasound as a complementary imaging method. Although urothelial neoplasms in the younger age group may recur, these events are typically benign (papilloma) or low-grade lesions. PUNLMP seems to have excellent long-term survival (Fine et al. 2005; Alanee and Shukla 2009).

References

Ahmed HU, Arya M, Levitt G et al (2007) Part I: primary malignant non-Wilms' renal tumors in children. Lancet Oncol 8:730–737

Alanee S, Shukla AR (2009) Bladder malignancies in children aged < 18 years: results from the Surveillance, Epidemiology and End results database. BJU Int 106:557–560

Ammerlaan AC, Ararou A, Houben MP, Baas F, Tijssen CC, Teepen JL, Wesseling P, Hulsebos TJ (2007) Long-term survival and transmission of INI1-mutation via nonpenetrant males in a family with rhabdoid tumour predisposition syndrome. Br J Cancer 18:18

Argani P, Ladanyi M (2003) Recent advances in paediatric renal neoplasia. Adv Anat Pathol 10:243–260

Argani P, Ladanyi M (2005) Translocation carcinomas of the kidney. Clin Lab Med 25:363–378

Argani P, Ladanyi M (2006) The evolving story of renal translocation carcinomas. Am J Clin Pathol 126:332–334

Argani P, Perlman EJ, Breslow NE, Browning NG, Green DM, D'Angio GJ, Beckwith JB (2000) Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms Tumor Study Group Pathology Center. Am J Surg Pathol 24:4–18

Argani P, Antonescu CR, Illei PB et al (2001a) Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinct tumor entity previously included among renal cell carcinomas of children and adolescents. Am J Pathol 159:179–192

Argani P, Hawkins A, Griffin CA et al (2001b) A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. Am J Pathol 158:2089–2096

Argani P, Lui MY, Couturier J et al (2003) A novel CLTC-TFE3 gene fusion in pediatric renal cell adenocarcinoma with t(X;17)(p11.2;q23). Oncogene 22:5374–5378

Argani P, Laé M, Hutchinson B et al (2005) Renal carcinoma with the t(6;11)(p21;q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. Am J Surg Pathol 29:230–240

Argani P, Laé M, Ballard ET, Amin M et al (2006) Translocation carcinomas of the kidney after chemotherapy in childhood. J Clin Oncol 24:1530–1534

Argani P, Olgac S, Tickoo SK et al (2007) Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am J Surg Pathol 31:1149–1160

Arroyo MR, Green DM, Perman EJ et al (2001) The spectrum of metanephric adenofibroma and related lesions. Am J Surg Pathol 25:433–444

Athale UH, Duckworth J, Odame I, Barr R (2009) Childhood atypical teratoid rhabdoid tumor of the central nervous system: a meta-analysis of observational studies. J Pediatr Hematol Oncol 31:651–663

Baek M, Jung JY, Kim JJ, Park KH, Ryu DS (2010) Characteristics and clinical outcomes of renal cell carcinoma in children: a single center experience. Int J Urol 17(8):737–740

Barroca H (2008) Fine needle biopsy and genetics, two allied weapons in the diagnosis, prognosis, and target therapeutics of solid pediatric tumors. Diagn Cytopathol 36:678–684

Bellmunt J, Guix M (2009) The medical management of metastatic renal cell carcinoma: integrating new guidelines and recommendations. BJU Int 103:572–577

Berger A, Kim C, Hagstrom N, Ferrer F (2007) Succesful preoperative treatment of pediatric bladder inflammatory myofibroblastic tumor with anti-inflammatory therapy. Urology 70(372):e13–e15

Biegel JA (2006) Molecular genetics of atypical teratoid/rhabdoid tumor. Neurosurg Focus 20:E11

Biegel JA, Allen CS, Kawasaki K, Shimizu N, Budarf ML, Bell CJ (1996) Narrowing the critical region for a rhabdoid tumor locus in 22q11. Genes Chromosomes Cancer 16:94–105

Biegel JA, Kalpana G, Knudsen ES, Packer RJ, Roberts CW, Thiele CJ, Weissman B, Smith M (2002a) The role of INI1 and the SWI/SNF complex in the development of rhabdoid tumors: meeting summary from the workshop on childhood atypical teratoid/rhabdoid tumors. Cancer Res 62:323–328

Biegel JA, Tan L, Zhang F, Wainwright L, Russo P, Rorke LB (2002b) Alterations of the hSNF5/INI1 gene in central nervous system atypical teratoid/rhabdoid tumors and renal and extrarenal rhabdoid tumors. Clin Cancer Res 8:3461–3467

Blom JH, van Poppel H, Maréchal JM et al (2008) Radical nephrectomy with and without lymph-node dissection: final results of the European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol 55:28–34

Brownlee NA, Perkins LA, Stewart W, Jackle B, Pettenati MJ, Koty PP, Iskandar SS, Garvin AJ (2007) Recurring translocation (10;17) and deletion (14q) in clear cell sarcoma of the kidney. Arch Pathol Lab Med 131:446–451

Bruder E, Passera O, Harms D et al (2004) Morphologic and molecular characterization of renal cell carcinoma in children and young adults. Am J Surg Pathol 28:1117–1132

Brugarolas J (2007) Renal-cell carcinoma – molecular pathways and therapies. N Engl J Med 356:185–187

Bukowski RM (2010) Pazopanib: amultikinase inhibitor with activity in advanced renal cell carcinoma. Expert Rev Anticancer Ther 10:635–645

Camparo P, Vasiliu V, Molinie V et al (2008) Renal translocation carcinomas: clinicopathologic, immunohistochemical, and gene expression profiling analysis of 31 cases with a review of the literature. Am J Surg Pathol 35:656–670

Carcao MD, Taylor GP, Greenberg ML et al (1998) Renal-cell carcinoma in children: a different disorder from its adult counterpart? Med Pediatr Oncol 31:153–158

Chi SN, Zimmerman MA, Yao X, Cohen KJ, Burger P, Biegel JA, Rorke-Adams LB, Fisher MJ, Janss A, Mazewski C, Goldman S, Manley PE, Bowers DC, Bendel A, Rubin J, Turner CD, Marcus KJ, Goumnerova L, Ullrich NJ, Kieran MW (2008) Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. J Clin Oncol 8:8–14

Ciftci AO, Talim B, Senocak ME et al (2000) Renal oncocytoma: diagnostic and therapeutic aspects. J Pediatr Surg 35:1396–1398

Cook A, Lorenzo AJ, Salle JL et al (2006) Pediatric renal cell carcinoma: single institution 25-year case series and initial experience with partial nephrectomy. J Urol 175:1456–1460

Corey SJ, Andersen JW, Vawter GF, Lack EE, Sallan SE (1991) Improved survival for children with anaplastic Wilms' tumors. Cancer 68:970–974

Cutcliffe C, Kersey D, Huang CC, Zeng Y, Walterhouse D, Perlman EJ, Renal Tumor Committee of the Children's Oncology Group (2005) Clear cell sarcoma of the kidney: up-regulation of neural markers with activation of the sonic hedgehog and Akt pathways. Clin Cancer Res 11:7986–7994

D'Angio GJ, Breslow N, Beckwith JB, Evans A, Baum H, deLorimier A, Fernbach D, Hrabovsky E, Jones B, Kelalis P et al (1989) Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. Cancer 64:349–360

Davis CJ Jr, Mostofi FK, Sesterhenn IA (1995) Renal medullary carcinoma. The seventh sickle cell nephropathy. Am J Surg Pathol 19:1–11

Eble JN, Sauter G, Epstein JI, Sesterhenn IA (2004) Pathology and genetics of tumours of the urinary system and male genital organs. In: Kleihue P, Sobin L (eds) World Health Orgnization classification of tumors. IARC Press, Lyon, pp 89–123

Escudier B (2010a) Chemo-immunotherapy in RCC: the end of a story. Lancet 375:613–614

Escudier B (2010b) Sunitinib for the management of advanced renal cell carcinoma. Expert Rev Anticancer Ther 10:305–317

Escudier B, Kataja V (2010) Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(suppl 5):v137–v139

Escudier B, Eisen T, Stadler WM et al (2007a) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125–134

Escudier B, Pluzanska A, Koralewski P et al (2007b) Bevacizumab plus interferon alfa-2a fro treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 370:2103–2111

Escudier B, Eisen T, Stadler WM et al (2009) Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 27:3312–3318

Escudier B, Bellmunt J, Négrier S et al (2010) Phase III trial of bevacizumab plus interferon alfta-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 28:2144–2150

Estrada CR, Suthar AM, Eaton SH et al (2005) Renal cell carcinoma: Children's Hospital Boston experience. Urology 66:1296–1300

Ficarra V (2007) Open radical nephrectomy versus open partial nephrectomy: is it still an issue? Eur Urol 51:593–595

Fine SW, Humphrey PA, Dehner LP et al (2005) Urothelial neoplasms in patients 20 years or younger: a clinicopathological analysis using the World Health Organization 2004 bladder consensus classification. J Urol 174:1976–1980

Frühwald MC, Hasselblatt M, Wirth S, Köhler G, Schneppenheim R, Subero JI, Siebert R, Kordes U, Jürgens H, Vormoor J (2006)

Non-linkage of familial rhabdoid tumors to SMARCB1 implies a second locus for the rhabdoid tumor predisposition syndrome. Pediatr Blood Cancer 47:273–278

Geller JI, Dome JS (2004) Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. Cancer 101:1575–1583

Geller JI, Argani P, Adeniran A et al (2008) Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer 112:1607–1616

Giedl J, Wild PJ, Stoehr R et al (2006) Urothelial neoplasms in individuals younger than 20 years show very few genetic alterations and have a favourable clinical outcome. Verh Dtsch Ges Pathol 90:253–263

Gill IS, Aron M, Gervais DA, Jewett MAS (2010) Small renal masses. N Engl J Med 362:624–634

Graf N, Reinhard H, Aliani S et al (2003) Wilms tumour with or without tumour related symptoms at diagnosis. Med Pediatr Oncol 41:266, O036 (Abstract)

Gripp KW, Lin AE (2005) Tumor predisposition in Costello syndrome. Am J Med Genet C Semin Med Genet 137C(1):72–77

Grundy RG, Hutton C, Middleton H, Imeson J, Pritchard J, Kelsey A, Marsden HB, Vujanic GM, Taylor RE, United Kingdom Children's Cancer Study Group (2004) Outcome of patients with stage III or inoperable WT treated on the second United Kingdom WT protocol (UKWT2); a United Kingdom Children's Cancer Study Group (UKCCSG) study. Pediatr Blood Cancer 42:311–319

Gururangan S, Bowman LC, Parham DM, Wilimas JA, Rao B, Pratt CB, Douglass EC (1993) Primary extracranial rhabdoid tumors: clinicopathologic features and response to ifosfamide. Cancer 71:2653–2659

Gutjahr P, Kaatsch P, Spaar HJ et al (1990) Klinik, Therapie und Prognose bei 373 Kindern mit Wilms-Tumoren – Ergebnisse der bundesweiten Studie 1980–1988. Akt Uro 121:132–141

Haas JE, Palmer NF, Weinberg AG, Beckwith JB (1981) Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children. Hum Pathol 12:646–657

Hirose M, Yamada T, Toyosaka A, Hirose T, Kagami S, Abe T, Kuroda Y (1996) Rhabdoid tumor of the kidney: a report of two cases with respective tumor markers and a specific chromosomal abnormality, del(11p13). Med Pediatr Oncol 27:174–178

Hoenig DM, McRae S et al (1996) Transitional cell carcinoma of the bladder in the pediatric patient. J Urol 156:203

Houben CH, Chan A, Lee KH et al (2007) Inflammatory myofibroblastic tumor of the bladder in children: what can be expected? Pediatr Surg Int 23:815–819

Huang CC, Cutcliffe C, Coffin C, Sorensen PH, Beckwith JB, Perlman EJ, Renal Tumor Committee of the Children's Oncology Group (2006) Classification of malignant pediatric renal tumors by gene expression. Pediatr Blood Cancer 46:728–738

Hudes G, Carducci M, Tomczak P et al (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271–2281

Indolfi P, Terenziani M, Casale F et al (2003) Renal cell carcinoma in children: a clinicopathologic study. J Clin Oncol 21:530–535

Jackson EM, Sievert AJ, Gai X, Hakonarson H, Judkins AR, Tooke L, Perin JC, Xie H, Shaikh TH, Biegel JA (2009) Genomic analysis using high-density single nucleotide polymorphism-based oligonucleotide arrays and multiplex ligation-dependent probe amplification provides a comprehensive analysis of INI1/SMARCB1 in malignant rhabdoid tumors. Clin Cancer Res 15:1923–1930

Janson K, Nedzi LA, David O, Schorin M, Walsh JW, Bhattacharjee M, Pridjian G, Tan L, Judkins AR, Biegel JA (2006) Predisposition to atypical teratoid/rhabdoid tumor due to an inherited INI1 mutation. Pediatr Blood Cancer 47:279–284

Joshi DD, Banerjee T (2008) Vascular endothelial growth factor (VEGF) receptor antibody bevacizumab (avastin) induces regression of renal cell carcinoma in an adolescent resulting in residual tumorectomy. Pediatr Blood Cancer 50:903–904

Judkins AR (2007) Immunohistochemistry of INI1 expression: a new tool for old challenges in CNS and soft tissue pathology. Adv Anat Pathol 14:335–339

Kidd JM (1970) Exclusion of certain renal neoplasms from the category of Wilms tumor [abstract]. Am J Pathol 58:16a

Kordes U, Gesk S, Frühwald MC, Graf N, Leuschner I, Hasselblatt M, Jeibmann A, Oyen F, Peters O, Pietsch T, Siebert R, Schneppenheim R (2010) Clinical and molecular features in patients with rhabdoid tumor predisposition syndrome. Genes Chromosomes Cancer 49:176–181

Kumar D, Sharma P, Agarwala S et al (2010) Pediatric renal non Hodgkin lymphoma with inferior cava thrombosis. J Pediatr Hematol Oncol 32:147–149

Kusumakumary P, Chellam VG, Rojymon J, Hariharan S, Krishnan NM (1997) Late recurrence of clear cell sarcoma of the kidney. Med Pediatr Oncol 28:355–357

Lerena J, Krauel L, Garcia-Aparicio L et al (2010) Transitional cell carcinoma of the bladder in children and adolescents: six-cases series and review of the literature. J Pediatr Urol 6:481–485

Lopez-Beltran A, Carrasco JC, Cheng L, Scarpelli M, Kirkali Z, Montironi R (2009) 2009 update on the classification of renal epithelial tumors in adults. Int J Urol 16:432–443

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109

Magnani C, Gatta G, Corazziari I et al (2001) Childhood malignancies in the EUROCARE study: the database and the methods of survival analysis. Eur J Cancer 37:678–686

Malouf GG, Camparo P, Oudard S et al (2010) Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network. Ann Oncol 21(9):1834–1838

Margulis V, Wood CG (2008) The role of lymph node dissection in renal cell carcinoma: the pendulum swings back. Cancer J 14:308–314

Marsden HB, Lawler W (1980) Bone metastasizing renal tumor of childhood. Histopathological and clinical review of 38 cases. Virchows Arch A Pathol Anat Histol 387:341–351

Miniati D, Gay AN, Parks KV et al (2008) Imaging accuracy and incidence of Wilms' and non-Wilms' renal tumors in children. J Pediatr Surg 43:1301–1307

Mitchell C, Pritchard-Jones K, Shannon R, Hutton C, Stevens S, Machin D, Imeson J, Kelsey A, Vujanic GM, Gornall P, Walker J, Walker J, Taylor R, Sartori P, Hale J, Levitt G, Messahel B, Middleton H, Grundy R, Pritchard J, United Kingdom Cancer Study Group (2006) Immediate nephrectomy versus preoperative chemotherapy in the management

of non-metastatic Wilms' tumour: results of a randomised trial (UKW3) by the UK Children's Cancer Study Group. Eur J Cancer 42:2554–2562

Motzer RJ, Hutson TE, Tomczak P et al (2007) Sunitinib versus inteferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115–124

Motzer RJ, Hutson TE, Tomczak P et al (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 27:3584–3590

Mou JW, Lee KH, Tam YH et al (2008) Urinary bladder pheochromocytoma, an extremely rare tumor in children: case report and review of the literature. Pediatr Surg Int 24:479–480

Niu ZB, Yang Y, Hou Y et al (2010) Lymphangioma of bladder. Urology 76(4):955–957

Parham DM, Weeks DA, Beckwith JB (1994) The clinicopathologic spectrum of putative extrarenal rhabdoid tumors. An analysis of 42 cases studied with immunohistochemistry or electron microscopy. Am J Surg Pathol 18:1010–1029

Pastore G, Znaor A, Spreafico F, Graf N et al (2006) Malignant renal tumours incidence and survival in European children (1978–1997): report from the automated childhood cancer information system project. Eur J Cancer 42:2103–2114

Patel R, Tery T, Ninan GK (2008) Transitional cell carcinoma of the bladder in first decade of life. Pediatr Surg Int 24:1265–1268

Proust F, Laquerriere A, Constantin B, Ruchoux MM, Vannier JP, Freger P (1999) Simultaneous presentation of atypical teratoid/rhabdoid tumor in siblings. J Neurooncol 43: 63–70

Radulescu VC, Gerrard M, Moertel C et al (2008) Treatment of recurrent clear cell sarcoma of the kidney with brain metastasis. Pediatr Blood Cancer 50:246–249

Ramphal R, Pappo A, Zielenska M et al (2006) Pediatric renal cell carcinoma: clinical, pathologic, and molecular abnormalities associated with the members of the MiT Transcription factor family. Am J Clin Pathol 126:349–364

Rao Q, Chen JY, Wang JD et al (2009) Renal cell carcinoma in children and young adults: clinicopathological, immunohistochemical, and VHL gene analysis of 46 cases with follow-up. Int J Surg Pathol 19(2):170–179

Reinhard H, Reinert J, Beier R, Furtwängler R, Alkasser M, Rutkowski S, Frühwald M, Koscielniak E, Leuschner I, Kaatsch P, Graf N (2008) Rhabdoid tumors in children: prognostic factors in 70 patients diagnosed in Germany. Oncol Rep 19:819–823

Renshaw MD (2005) Local lymph node involvement does not predict poor out come in pediatric renal cell carcinoma. Cancer 103:1317–1318

Rickert CH, Paulus W (2004) Chromosomal imbalances detected by comparative genomic hybridisation in atypical teratoid/rhabdoid tumours. Childs Nerv Syst 20:221–224, Epub 2004 Feb 4

Ries LAG, Melbert D, Krapcho M et al (eds) (2008) SEER cancer statistics review, 1975–2005. National Cancer Institute. National Cancer Institute, Bethesda

Rini BI, Campbell SC, Escudier B (2009) Renal cell carcinoma. Lancet 373:1119–1132

Roberts CW, Galusha SA, McMenamin ME, Fletcher CD, Orkin SH (2000) Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. Proc Natl Acad Sci USA 97:13796–13800

Roberts CW, Leroux MM, Fleming MD, Orkin SH (2002) Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene Snf5. Cancer Cell 2:415–425

Sausville JE, Hernandez DJ, Argani P et al (2009) Pediatric renal cell carcinoma. J Pediatr Urol 5:308–314

Schafernak KT, Yang XJ, Hsueh W, Leestma JL, Stagl J, Goldman S (2007) Pediatric renal cell carcinoma as second malignancy: reports of two cases and review of the literature. Can J Urol 14:3739–3744

Schenk JP, Engelmann D, Rohrschneider W et al (2004) Rhabdoid tumors of the kidney in childhood. Röfo 176:965–971

Schenk JP, Engelmann D, Zieger B et al (2005) [Radiologic differentiation of rhabdoid tumor from Wilms' tumor and mesoblastic nephroma]. Urologe A 44:155–161

Schuster AE, Schneider DT, Fritsch MK, Grundy P, Perlman EJ (2003) Genetic and genetic expression analyses of clear cell sarcoma of the kidney. Lab Invest 83:1293–1299

Scott RH, Walker L, Olsen ØE et al (2006) Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. Arch Dis Child 91:995–999

Sebire NJ, Vujanic GM (2009) Paediatric renal tumours: recent developments, new entities and pathological features. Histopathology 54:516–528

Seibel NL, Li S, Breslow NE et al (2004) Effect of duration of treatment on treatment outcome for patients with clear-cell sarcoma of the kidney: a report from the National Wilms' Tumor Study Group. J Clin Oncol 22:468–473

Seibel NL, Sun J, Anderson JR, et al (2006) Outcome of clear cell sarcoma of the kidney (CCSK) treated on the National Wilms Tumor Study-5 (NWTS) [Abstract]. J Clin Oncol 24(suppl 18): A-9000, 502s

Selle B, Furtwängler R, Graf N, Kaatsch P, Bruder E, Leuschner I (2006) Population-based study of renal cell carcinoma in children in Germany, 1980-2005: more frequently localized tumors and underlying disorders compared with adult counterparts. Cancer 107:2906–2914

Sevenet N, Sheridan E, Amram D, Schneider P, Handgretinger R, Delattre O (1999) Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. Am J Hum Genet 65:1342–1348

Shet T, Viswanathan S (2009) The cytological diagnosis of paediatric renal tumours. J Clin Pathol 62:961–969

Silberstein J, Grabowski J, Saltzstein SL, Kane CJ (2009) Renal cell carcinoma in the pediatric population: results from the California cancer registry. Pediatr Blood Cancer 52:237–241

Smets AM, de Kraker J (2010) Malignant tumours of the kidney: imaging strategy. Pediatr Radiol 40:1010–1018

Sotelo-Avila C, Gonzalez-Crussi F, deMello D, Vogler C, Gooch WM III, Gale G, Pena R (1986) Renal and extrarenal rhabdoid tumors in children: a clinicopathologic study of 14 patients. Semin Diagn Pathol 3:151–163

Soulières D (2009) Review of guidelines on the treatment of metastatic renal cell carcinoma. Curr Oncol 16 (suppl 1):67–70

Squire SE, Chan MD, Marcus KJ (2007) Atypical teratoid/rhabdoid tumor: the controversy behind radiation therapy. J Neurooncol 81:97–111, Epub 2006 Jul 20

Sun M, Lughezzani G, Perrotte P, Karakiewicz PI (2010) Treatment of metastatic renal cell carcinoma. Nat Rev Urol 7:327–338

Swartz MA, Karth J, Schneider DT et al (2002) Renal medullary carcinoma: clinical, pathological, immunohistochemical, and genetic analysis with pathogenetic implications. Urology 60:1083–1089

Taylor MD, Gokgoz N, Andrulis IL, Mainprize TG, Drake JM, Rutka JT (2000) Familial posterior fossa brain tumors of infancy secondary to germline mutation of the hSNF5 gene. Am J Hum Genet 66:1403–1406, Epub 2000 Mar 14

Tomlinson GE, Breslow NE, Dome J, Guthrie KA, Norkool P, Li S, Thomas PR, Perlman E, Beckwith JB, D'Angio GJ, Green DM (2005) Rhabdoid tumor of the kidney in the National Wilms' tumor study: age at diagnosis as a prognostic factor. J Clin Oncol 23:7641–76415

Touijer K, Jacqmin D, Kavoussi LR et al (2010) The expanding role of partial nephrectomy: a critical analysis of indications, results, and complications. Eur Urol 57:214–222

van den Heuvel-Eibrink MM, Grundy P, Graf N, Pritchard-Jones K, Bergeron C, Patte C, van Tinteren H, Rey A, Langford C, Anderson JR, de Kraker J (2008) Characteristics and survival of 750 children diagnosed with a renal tumor in the first seven months of life: a collaborative study by the SIOP/GPOH/SFOP, NWTSG, and UKCCSG Wilms tumor study groups. Pediatr Blood Cancer 50:1130–1134

Versteege I, Sevenet N, Lange J, Rousseau-Merck MF, Ambros P, Handgretinger R, Aurias A, Delattre O (1998) Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature 394:203–206

Vujanic GM, Sandstedt B, Harms D, Boccon-Gibod L, Delemarre JF (1996) Rhabdoid tumour of the kidney: a clinicopathological study of 22 patients from the International Society of Paediatric Oncology (SIOP) nephroblastoma file. Histopathology 28:333–340

Vujanic GM, Sandstedt B, Kelsey A, Sebire NJ (2009) Central pathology review in multicenter trials and studies: lessons from the nephroblastoma trials. Cancer 115:1977–1983

Wagner L, Hill DA, Fuller C, Pedrosa M, Bhakta M, Perry A, Dome JS (2002) Treatment of metastatic rhabdoid tumor of the kidney. J Pediatr Hematol Oncol 24:385–388

Waldron PE, Rodgers BM, Kelly MD, Womer RB (1999) Successful treatment of a patient with stage IV rhabdoid tumor of the kidney: case report and review. J Pediatr Hematol Oncol 21:53–57

Weeks DA, Beckwith JB, Mierau GW (1989) Rhabdoid tumor. An entity or a phenotype? Arch Pathol Lab Med 113:113–114

Wick MR, Ritter JH, Dehner LP (1995) Malignant rhabdoid tumors: a clinicopathologic review and conceptual discussion. Semin Diagn Pathol 12:233–248

Wiesbauer P (2008) Nephrogene Tumoren. Radiologe 48:932–939

Wiygul JB, Palmer L (2010) Isolated hemangioma causing gross painless hematuria in an adolescent male. Urology 76:463–464

Wu A, Kunju LP, Cheng L, Shah RB (2008) Renal cell carcinoma in children and young adults: analysis of clinicopathological, immunohistochemical and molecular characteristics with an emphasis on the spectrum of Xp11.2 translocation-associated and unusual clear cell subtype. Histopathology 53:533–544

Yossepowitch O, Dalbagni G (2002) Transitional cell carcinoma of the bladder in young adults: presentation, natural history and outcome. J Urol 168:61

Zhang F, Tan L, Wainwright LM, Bartolomei MS, Biegel JA (2002) No evidence for hypermethylation of the hSNF5/INI1 promoter in pediatric rhabdoid tumors. Genes Chromosomes Cancer 34:398–405

Zhuge Y, Cheung MC, Yang R et al (2010) Pediatric non-Wilms tumors: subtypes, survival, and prognostic indicators. J Surg Res 163:257–263

Zimmerman MA, Goumnerova LC, Proctor M, Scott RM, Marcus K, Pomeroy SL, Turner CD, Chi SN, Chordas C, Kieran MW (2005) Continuous remission of newly diagnosed and relapsed central nervous system atypical teratoid/rhabdoid tumor. J Neurooncol 72:77–84

Breast Cancer

41

Dominik T. Schneider

Contents

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Breast cancer during adolescents and in particular childhood is exceedingly rare. Epidemiological data from the SEER registry indicate that by far less than 1% of breast cancers develop in children and adolescents. Over a 20-year period, 75 patients up to the age of 19 years have been identified with malignant breast tumors (Gutierrez et al. 2008). According to the most recent analysis of SEER data on rare tumors registered between 1973 and 2006, 10 carcinomas of the breast have been diagnosed in the age group 0–14 years and 55 among adolescents of 15–19 years of age, respectively (see Chap. 2). Based on these data, approximately two children and adolescents with breast cancer can be expected per year in the USA.

The vast majority of breast masses in children and adolescents are benign, ranging from the frequent postnatal breast hypertrophy to peripubertal changes. Nevertheless, the detection of a "lump in the breast" may be disconcerting for the patients and their parents, given their knowledge of the high overall frequency of breast cancer in adults. In this situation, the pediatric oncologist may also be involved in the diagnostic considerations and should be aware about the most important differential diagnoses. Considering the rarity of true epithelial breast cancer in children, the diagnosis and treatment of malignant breast cancer should be planned in a multidisciplinary setting that might include: experienced breast cancer surgeon or gynecology oncologist, a pediatric oncologist, and medical oncologist who specialize in treatment of breast cancer.

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41.1 Breast Lesions in Children and Adolescents: Clinical Approach and Differential Diagnosis

The clinical assessment and examination in case of breast enlargement may be difficult due to a broad variability of the glandular size during childhood and puberty. In general, breast masses in boys mostly represent gynecomastia, benign tumors, or metastatic tumors (Welch et al. 2004). Tumors arising from the glandular tissue predominantly occur in girls.

History and examination should include time of onset, signs of infection, pain, discharge, and uni-/bilateral presentation. Postnatal breast hypertrophy and, in rare cases, mastitis are easy to diagnose and are usually not associated with significant complications (Stricker et al. 2005). In contrast, the differential diagnosis of breast changes in peripubertal girls is more complicated. The most frequent reasons for uni- or bilateral breast enlargement are premature (prior to the 8th year of life) or mature thelarche, which presents as enlargement of the glandular tissue below the areola. Thelarche may be earlier in association with obesity and ethnic background (Rosenfield et al. 2009). Premature thelarche may occur during toddler age. Estrogens are normal, and children do not show additional signs of pubertal development such as adrenarche or increased growth velocity. Thus, premature thelarche should be distinguished from true precocious puberty by the presence of additional signs of pubertal development. In the latter, a diagnostic work-up that includes endocrinologic testing and abdominal and pelvic ultrasound is indicated to exclude endocrinologic or ovarian disorders (e.g., juvenile granulosa cell tumor, see Chap. 39).

During infancy and early childhood, subcutaneous breast tumors may represent vascular tumors such as lymphangiomas and hemangiomas (Nagar et al. 1992; Welch et al. 2004). These tumors do not show a female sex restriction. They can be distinguished from glandular tumors with ultrasound (and in rare cases MRI). Furthermore, leukemic or lymphoma infiltrates, neurofibromas, mesenchymal tumors (such as rhabdomyosarcoma), or bone tumors of the ribs (e.g., Ewing sarcoma in older children and adolescents) may develop in close proximity, but rarely within the breast (Bongiorno et al. 2010; Conter et al. 1992; Chung et al. 2009; Chateil et al. 1998). More commonly, these tumors are located outside and not restricted to the glandular tissue. These entities will be distinguished histopathologically.

With the onset of puberty, fibrocystic mastopathy, fibroadenoma, breast trauma, and infection are the most frequent causes of a breast mass (Chung et al. 2009). The most common differential diagnoses are listed in Table 41.1. In most cases, diagnosis may be established based on medical history and clinical appearance. Of note, mammography has only low diagnostic impact due to dense glandular tissue in adolescents (Brand et al. 1993; Chateil et al. 1998). Therefore, the use of mammography should be very restrictive in (pre-)/pubertal girls (Ashley et al. 1989). Instead, ultrasound or MRI is required. Fine needle aspiration (FNA) for cytologic evaluation is often done and shows superior sensitivity compared to imaging only (Ashley et al. 1989). While this method is sufficient for most breast carcinomas, it is not adequate for sarcomas, such as angiosarcoma, which is easily missed. The value of FNA has also not been confirmed in children and adolescents, in whom adenocarcinoma is more infrequent, and therefore, differential diagnosis is different than in adults. Thus, a fine-needle biopsy may show better sensitivity and specificity than a punctate that is evaluated cytologically only. In equivocal cases, histologic examination of an open biopsy is required for diagnostic assessment (for example, angiosarcoma). In some rare cases (e.g., intraductal papilloma), diagnosis can be established through cytologic evaluation of nipple discharge.

Some of these disorders are related to the pubertal and hormone-sensitive breast development. Thus, fibrocystic changes are commonly observed in adolescents and women of reproductive age (Greydanus et al. 2006; Neinstein et al. 1993). They present as ill-defined fibrotic hardening of the breast, most commonly in the outer upper quadrant. Lesions are usually painless, but during the late menstrual cycle, they may be painful. Pain usually responses well to ibuprofen. These changes are thought to be the result of endocrinologic imbalances between estrogens and progesterones. Treatment may also include contraceptive drugs with estrogen component. There is a chance for resolution of these fibrocystic changes over time (Neinstein et al. 1993).

Fibroadenoma (juvenile) constitutes the most prevalent tumor lesion of the breast in adolescents (Chung et al. 2009; Greydanus et al. 2006; Simmons 1992). It may present as well circumscribed masses of

Table 41.1 Differential diagnosis of breast lesions according to age

Age	Diagnosis	Clinical hallmarks and diagnostic assessment
Neonate	Breast hypertrophy	Medical history
	Mastitis	Medical history, signs of local infection
	Hemangioma, lymphangioma	Clinical appearance. Ultrasound (Doppler)
Prepubertal	Mesenchymal tumors	Not restricted to breast gland. Ultrasound, biopsy
	(Pre-) mature thelarche	Medical history, uni- or bilateral breast enlargement below the areola. Ultrasound
Pubertal	Fibrocystic mastopathy	Painful breast during menses, improvement during menstruation, sometimes discharge. Ultrasound
	Fibroadenoma (juvenile)	Asymptomatic circumscribed, rubbery, and mobile breast lump in upper outer quadrant. Ultrasound: avascular echo, biopsy, excision in case of giant fibroadenoma (>5 cm)
	Intraductal papilloma	Bloody nipple discharge, well-circumscribed nodule. Ultrasound, cytology of nipple discharge
	Cystosarcoma phyllodes	Painless mass, sometimes with nipple discharge. Ultrasound: lobulation, heterogeneous echo, no calcification, excision
	Montgomery tubercles	Obstruction and/or inflammation of periareolar glands
	Duct ectasia	Distention of subareolar ducts, nipple discharge, sometimes blueish discolored subareolar lump
	Fat necrosis	Most commonly posttraumatic, fibrotic nodule
	Neurofibroma	Other diagnostic signs of NF-1: neurofibroma, café-au-lait spots, freckling, etc.
	Metastases	e.g., leukemia, Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma
	Primary breast cancer	Irregular mass, indolent, fixed or not, nipple discharge, peau d'orange, enlarged axillary lymph nodes. Ultrasound, MRI, biopsy!

rubber consistency. Most tumors are asymptomatic and reach a size of 2–3 cm, but some of these estrogen sensitive tumors may grow to "giant fibroadenoma," causing local pain. Fibroadenomas present as solid avascular masses on ultrasound. Histologically, these tumors consist of densely proliferating glandular stroma. Of note, a significant proportion of fibroadenoma during puberty shows spontaneous regression over time, and only a few fibroadenomas may transform into malignant tumors (Carty et al. 1995; Tea et al. 2009). Therefore, smaller juvenile fibroadenoma may be followed for 2–3 menstrual cycles. However, if they continuously grow, surgical resection should be considered, since the surgical therapy may be more extensive if the tumors are larger (Greydanus et al. 2006). In general, if tumors are larger than 5 cm at diagnosis, symptomatic, continuously grow, or persist to adulthood, excision is justified.

Other genuine breast tumors, such as phyllodes tumor (syn. cystosarcoma phyllodes) and intraductal papilloma, more commonly develop during adulthood and rarely arise in adolescents or children. Diagnostic assessment and treatment should be managed with an interdisciplinary approach that includes the gynecologist and pediatrician. In the SEER survey of malignant breast cancers, phyllodes tumors contributed half of the malignant primary breast tumors (Gutierrez et al. 2008). These tumors are biphasic tumors that include both an epithelial and a stromal component. They commonly present in the upper outer quadrant and may develop a considerably size (in average 8–10 cm) (Greydanus et al. 2006). They frequently present with a leaf-like lobulated structure. The local relapse rate is low (approx. 10%), provided that the lobulated tumor is excised completely. The frequency of metastases is lower (<5%) (Chen et al. 2005).

"True" primary breast cancer in children and adolescents is exceedingly rare compared to these benign lesions (Gutierrez et al. 2008; Tea et al. 2009). The most common clinical finding is a hard, often (but not always) fixed, indolent, and irregular mass. If the tumor grows subcutaneously, the skin may show a peau d'orange appearance. Nipple discharge may result from intraductal or subareolar growth. The clinical examination must always include the axillary lymph nodes to exclude lymph node metastases. Again,

Table 41.2 Diagnostic assessment in primary breast cancer

Procedure	Specific question
Medical history	Duration of symptoms, nipple discharge, pubertal and medical history Family history of breast and ovarian cancer Previous malignancy, in particular irradiation to chest
Physical examination	Location, consistency, size, mobility, pain, inflammation, skin changes, nipple discharge, nipple appearance Axillary lymphadenopathy Hepatomegaly
Blood count	Signs of bone marrow failure/ metastases
Liver enzymes, AP, LDH	Signs of liver metastases, bone metastases, unspecific tumor marker. Other tumor markers are not required (ASCO 1998)
Ultrasound	Cystic vs. solid, size, vascularity, lymph nodes, etc.
MRI	Cystic vs. solid, size, vascularity, lymph nodes, contralateral breast, etc.
CT thorax	Lung metastases
Bone scintigraphy	Skeletal metastases
Abdom. ultrasound	Liver metastases
Biopsy/excision	FNA or biopsy. Histology, hormone receptor status, HER2 expression and/or *HER2* amplification

Mammography is not recommended

mammography is not indicated due to its diagnostic inaccuracy. Radiographic imaging includes imaging and MRI. Lungs must be screened for metastases with CT. Moreover, abdominal ultrasound, bone scintigraphy, and cranial MRI (in case of neurological signs) are indicated (Table 41.2).

The most difficult decision is whether to perform diagnostic and/or therapeutic maneuvers in children and adolescents with breast mass. In most small asymptomatic breast masses, lesions can be observed for at least two menstrual cycles (Templeman and Hertweck 2000). They may also be evaluated with fine needle aspiration (FNA). This maneuver may even be therapeutic in cystic lesions. Surgical resection or biopsy may be indicated if the lesions are suspicious of malignancy (e.g., based on physical examination (skin or nipple changes etc.), medical history of previous chest irradiation or familial breast cancer at young age), or if lesions continuously grow beyond 5 cm in diameter. If a solid lesion persists (longer than two menstrual cycles) and shows no signs of regression, histologic verification is indicated (Ashley et al. 1989).

41.2 Breast Cancer in Adults: Current Concepts

In adult women, breast cancer is the most frequent cancer and the second most common cause of cancer death in women in western countries. The median age at diagnosis is approximately 60 years. The risk of women to develop breast cancer during their lifetime is approximately 10–15%. During the fifth and sixth decade of life, breast cancer is the most frequent cause of death in western countries, making this cancer a major issue in clinical care, cancer research, and health policy. The incidence of breast cancer has been rising since 1970, while the mortality is slowly declining. Clinical and epidemiological studies indicate that age constitutes an independent prognostic factor, with young patients being at a higher risk.

Approximately 5–10% of all breast cancers are based on hereditary predisposition. Among these, mutations of *BRCA1* and *BRCA2* are most frequent. However, they are found in only 40–50% of patients with familial breast cancer. In patients with proven BRCA1/2 mutations, self-examination and early onset of clinical and sonographic screening are advocated starting in early adulthood (Antoniou et al. 2003; Ashley et al. 1989).

Data from long-term survivors of childhood cancer indicate that the risk of breast cancer is increased after irradiation to the thorax, e.g., for Hodgkin's lymphoma (Henderson et al. 2010). There is an obvious correlation between radiation dose to the breasts and the risk of later breast cancer. The risk does not plateau over time.

41.3 Diagnosis and Treatment

Detailed guidelines for diagnosis and treatment of breast cancer are beyond the scope of this chapter. Sufficient guidelines are available from several international and national oncology groups. One example is the American Society of Clinical Oncology (ASCO) guidelines (www.asco.org). Briefly, standard diagnostic studies for potential breast cancer include both mammography (in adults) and MRI.

In the USA, diagnosis is most often confirmed by FNA or biopsy (Fig. 41.1). Molecular studies and endocrine receptor studies will help inform treatment strategy in particular with regard to targeted and endocrinologic treatment. Sentinel node lymph node biopsy constitutes an integral part of treatment planning. Serological tumor marker evaluation is not recommended (ASCO 1998).

Modern surgical therapy of breast cancer aims for breast conserving local tumor resection. However, according to an analysis of two-pooled European studies, premenopausal patients tend to have a higher risk of local recurrence after breast conserving resection than postmenopausal patients. In addition, extensive intraductal growth was also associated with increased risk of local recurrence after breast conserving surgery. The risk of local recurrence did not correlate with age if mastectomy was performed. Nevertheless, conservative surgery does not show an adverse effect on survival (Voogd et al. 2001).

Adjuvant treatment includes radiotherapy, chemotherapy, and endocrinologic and targeted therapy. The risk of distant recurrence correlates with age <35 years, increasing tumor size, low histologic differentiation, vascular invasion, resection margins, and nodal status (Voogd et al. 2001). Based on these and comparable data from other study groups, risk groups for treatment stratification have been defined during the St. Gallen consensus conferences on early breast cancer (Goldhirsch et al. 2007; Goldhirsch et al. 2009). Considering the high risk of recurrence even in stage I, almost all patients younger than 35 years are eligible for adjuvant therapy – even despite the risk of long-term sequelae such as early menopause, impaired fertility, osteoporosis, and secondary cancers.

Radiotherapy serves to reduce the risk of local recurrences, including lymph node metastases, and is mostly indicated after breast conserving therapy. The mode of adjuvant systemic treatment depends on the immunohistochemical and molecular profile of the tumor. In estrogen-receptor-negative tumors, chemotherapy is administered. In receptor-positive tumors, tamoxifen (+/– chemotherapy) significantly reduces the risk of relapse. New perspectives have been opened by the introduction of epidermal growth factor receptor antibodies (e.g., trastuzumab, Herceptin®) that target tumors with *HER2* overexpression, caused by *HER2* amplification.

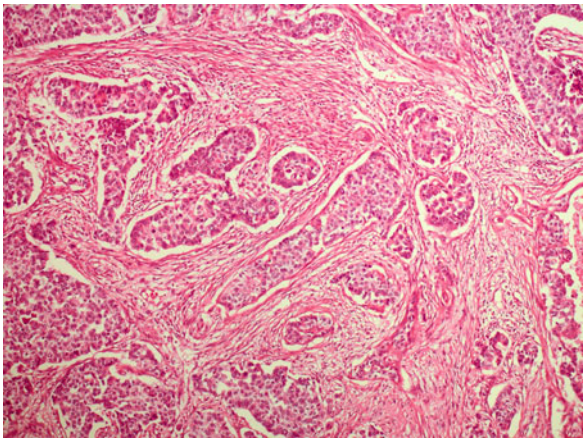

Fig. 41.1 Poorly differentiated invasive ductal carcinoma in a 35-year-old female (H&E) (Provided by Professor Lorenzen, Dortmund)

41.4 Management of Breast Cancer in Children and Adolescents

The clinical picture of breast cancer in children and adolescents differs from that in adults. Carcinoma in situ is exceedingly rare, while the most common type in childhood is the "secretory carcinoma." In the SEER data, females less than 19 years of age had 15% carcinoma in situ, 55% carcinomas, and 45% sarcomas (Gutierrez et al. 2008). Most of the sarcomas were phyllodes tumors (syn. cystosarcoma phyllodes). The choice of FNA or biopsy should be carefully considered in these young patients, since even FNA may sometimes result in cosmetic damage to the developing breast (Greydanus et al. 2006).

Most phyllodes tumors in children and adolescents (provided the small data of patients reported to date) are characterized by indolent clinical behavior, low tendency to develop distant metastases, and hence, they have a more favorable prognosis.

If true invasive ductal carcinoma is diagnosed, prognosis is more unfavorable, since these tumors may often show poor histologic differentiation, high proliferative activity, and a tendency to lymphovascular invasion. In large studies, young age (i.e., younger than 35 years) is an independent adverse prognostic factor (de la Rochefordiere et al. 1993). Thus, adolescents and adults with invasive ductal carcinoma tend to have larger and more advanced tumors with a longer history than elderly patients. Perhaps, this may be explained

by the lack of self-examination in this age group. Overall survival is also poorer than in older patients (de la Rochefordiere et al. 1993). Of note, breast cancer in young patients may show different immunohistochemical and genetic profiles compared to older patients. Tumors in younger patients are more often estrogen receptor-negative, grade 3, while the frequency of *HER2* overexpression appears to be comparable. However, even in case of positive receptor status, response to treatment and prognosis in young patients is worse than in older patients (>35 years) (Colleoni et al. 2006).

Therefore, therapy of breast carcinoma includes wide excision and assessment of axillary lymph nodes, as discussed above. In young patients, prognosis in stage I breast cancer is not satisfactory. If young patients are treated according to a "watch-and-wait" strategy, half of patients show tumor progression. Therefore, adjuvant treatment should be considered for almost all patients under the age of 35 years (Goldhirsch et al. 2007).

Therapeutic decisions regarding hormonal, targeted, and cytostatic treatment should be made after interdisciplinary consultation and under consideration of the pathologic stage, immunohistochemical and genetic profile of the tumor. Anthracycline-based combination regimens, often in combination with cyclophosphamide, currently constitute the most commonly applied chemotherapy regimen. Since the nineties of the last century, taxane-based regimens have also been evaluated and have also proven effective (e.g., combination of anthracycline, cyclophosphamide, and taxan) (Bria et al. 2006). They are currently considered standard therapy for nodal positive breast cancer. Endocrinologic treatment typically utilizes tamoxifen. The introduction of the *HER*2 inhibitor trastuzumab constitutes one of the most significant therapeutic progress in the last decade. Since the St. Gallen conference in 2009, trastuzumab in combination with chemotherapy is recommended for HER2 positive tumors larger than 1 cm (Goldhirsch et al. 2009). Optimal results have been obtained if trastuzumab has been applied in combination with anthracyclines, cyclophosphamide, and taxan and if administration of trastuzumab was concurrent to taxan.

Since the field of cytostatic, endocrinologic, and targeted treatment of breast cancer is rapidly developing, it is recommended that the therapy of children and adolescents be planned and performed by a multidisciplinary team, including a gynecooncologic breast surgeon, gynecooncologist, radiotherapist, medical oncologist, and pediatric oncologist. Currently, using such an interdisciplinary approach, a 5-year survival rate greater than 70% can be expected for adolescents and young adults with invasive breast cancer.

References

American Society of Clinical Oncology (ASCO) (1998) 1997 update of recommendations for the use of tumor markers in breast and colorectal cancer. Adopted on November 7, 1997 by the American Society of Clinical Oncology. J Clin Oncol 16:793–795

Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72:1117–1130

Ashley S, Royle GT, Corder A, Herbert A, Guyer PB, Rubin CM, Taylor I (1989) Clinical, radiological and cytological diagnosis of breast cancer in young women. Br J Surg 76:835–837

Bongiorno MR, Doukaki S, Arico M (2010) Neurofibromatosis of the nipple-areolar area: a case series. J Med Case Reports 4:22

Brand IR, Sapherson DA, Brown TS (1993) Breast imaging in women under 35 with symptomatic breast disease. Br J Radiol 66:394–397

Bria E, Nistico C, Cuppone F, Carlini P, Ciccarese M, Milella M, Natoli G, Terzoli E, Cognetti F, Giannarelli D (2006) Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. Cancer 106:2337–2344

Carty NJ, Carter C, Rubin C, Ravichandran D, Royle GT, Taylor I (1995) Management of fibroadenoma of the breast. Ann R Coll Surg Engl 77:127–130

Chateil JF, Arboucalot F, Perel Y, Brun M, Boisserie-Lacroix M, Diard F (1998) Breast metastases in adolescent girls: US findings. Pediatr Radiol 28:832–835

Chen WH, Cheng SP, Tzen CY, Yang TL, Jeng KS, Liu CL, Liu TP (2005) Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. J Surg Oncol 91:185–194

Chung EM, Cube R, Hall GJ, Gonzalez C, Stocker JT, Glassman LM (2009) From the archives of the AFIP: breast masses in children and adolescents: radiologic-pathologic correlation. Radiographics 29:907–931

Colleoni M, Rotmensz N, Peruzzotti G, Maisonneuve P, Orlando L, Ghisini R, Viale G, Pruneri G, Veronesi P, Luini A, Intra M, Cardillo A, Torrisi R, Rocca A, Goldhirsch A (2006) Role of endocrine responsiveness and adjuvant therapy in very young women (below 35 years) with operable breast cancer and node negative disease. Ann Oncol 17:1497–1503

Conter V, D'Angelo P, Rovelli A, Uderzo C, Jankovic M, Bratina G, Masera G (1992) Isolated breast relapse after allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia. Med Pediatr Oncol 20:165–168

de la Rochefordiere A, Asselain B, Campana F, Scholl SM, Fenton J, Vilcoq JR, Durand JC, Pouillart P, Magdelenat H, Fourquet A (1993) Age as prognostic factor in premenopausal breast carcinoma. Lancet 341:1039–1043

Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ (2007) Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 18:1133–1144

Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thurlimann B, Senn HJ (2009) Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 20:1319–1329

Greydanus DE, Matytsina L, Gains M (2006) Breast disorders in children and adolescents. Prim Care 33:455–502

Gutierrez JC, Housri N, Koniaris LG, Fischer AC, Sola JE (2008) Malignant breast cancer in children: a review of 75 patients. J Surg Res 147:182–188

Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, Diller LR, Constine LS, Smith RA, Mahoney MC, Morris EA, Montgomery LL, Landier W, Smith SM, Robison LL, Oeffinger KC (2010) Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. Ann Intern Med 152:444–455, W144-54

Nagar H, Marmor S, Hammar B (1992) Haemangiomas of the breast in children. Eur J Surg 158:503–505

Neinstein LS, Atkinson J, Diament M (1993) Prevalence and longitudinal study of breast masses in adolescents. J Adolesc Health 14:277–281

Rosenfield RL, Lipton RB, Drum ML (2009) Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics 123:84–88

Simmons PS (1992) Diagnostic considerations in breast disorders of children and adolescents. Obstet Gynecol Clin North Am 19:91–102

Stricker T, Navratil F, Sennhauser FH (2005) Mastitis in early infancy. Acta Paediatr 94:166–169

Tea MK, Asseryanis E, Kroiss R, Kubista E, Wagner T (2009) Surgical breast lesions in adolescent females. Pediatr Surg Int 25:73–75

Templeman C, Hertweck SP (2000) Breast disorders in the pediatric and adolescent patient. Obstet Gynecol Clin North Am 27:19–34

Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, van Tienhoven G, Andersen KW, Sylvester RJ, van Dongen JA (2001) Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J Clin Oncol 19:1688–1697

Welch ST, Babcock DS, Ballard ET (2004) Sonography of pediatric male breast masses: gynecomastia and beyond. Pediatr Radiol 34:952–957

Part IX

Rare Tumors of the Peripheral Nervous System

Rare Tumors of the Peripheral Nervous System

42

Bernadette Brennan, Carlos Rodriguez-Galindo, and Gianni Bisogno

Contents

42.1 Intra-adrenal (Pheochromocytoma) and Extra-adrenal Paraganglioma

Bernadette Brennan

42.1.1 Introduction and UK Registry Childhood Cancer Registry Data

The WHO in 2004 reclassified endocrine tumors and redefined pheochromocytoma as intra-adrenal paraganglioma and those tumors of extra-adrenal sympathetic or parasympathetic paraganglia as extra-adrenal paragangliomas (Pacak et al. 2007). Although rare in children, they are the commonest pediatric endocrine tumor with an instance of 1–2 per million (Stringel

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Table 42.1.1 Numbers of registrations by calendar period and tumor behavior

	Benign and unspecified	Malignant	Total
1971–1980	6	2	8
1981–1990	11	4	15
1991–2002	20	1	21

Unspecified are regarded as benign in ICD-O

Table 42.1.2 Numbers of registrations by age and sex, 1981–2002

	0–4 years	5–9 years	10–14 years	Male	Female	Total
Benign and unspecified	1	13	17	19	12	31
Malignant	0	2	3	3	2	5

et al. 1980). The majority of paragangliomas arise in the adrenal medulla (Lenders et al. 2005), but when they arise in extra-adrenal sites, they occur in decreasing order of frequency in the abdomen – in the organ of Zuckerkandl, pelvis, mediastinum, and the head and neck (Pacak et al. 2001). In the head and neck, they are mainly parasympathetic and nonsecreting with a specific entity arising in the carotid body – carotid body tumor – which is extremely rare in childhood (Deal et al. 1990). In childhood, they are often multiple or bilateral with 40% probably associated with an underlying genetic condition and very rarely are malignant (Krijger et al. 2006).

42.1.1.1 Pheochromocytomas in the United Kingdom National Registry of Childhood Tumors, 1971–2002

The registration of nonmalignant tumors has clearly been incomplete, especially before 1981. Detailed data therefore only covers the period 1981–2000 (Spoudeas and Harrison 2005) (Tables 42.1.1 and 42.1.2).

Pheochromocytoma was more common in older children, with boys more frequently affected (1.5:1).

Incidence of malignant pheochromocytoma was 0.02 per million children.

For benign and unspecified, a minimum estimate of incidence is 0.11 per million.

Among 31 children with benign or unspecified tumors, three were diagnosed at postmortem; no other deaths have been recorded.

Of five children registered with malignant pheochromocytoma, two died at intervals of 2 days and 14 months after diagnosis; the other three are alive with survival times between 3 and 22 years.

42.1.2 Clinical Presentation

In children the presentation can be very variable, but symptoms are mainly due to the excess catecholamine secretion (Caty et al. 1990; Criftci et al. 2001; Ein et al. 1997). Twice as many cases occur in boys than girls with a mean age of about 11 years at presentation, the majority presenting with hypertension which may be intermittent and not present in all cases (Barontini et al. 2006; Beltsevich et al. 2004; Ludwig et al. 2007). Other symptoms of catecholamine excess include headache, palpitations, excess sweatiness, weight loss, vomiting, anxiety, and behavioral problems (Haws et al. 2007).

Probably in nearly half of paragangliomas in childhood there will be a hereditary basis (Barontini et al. 2006; Krijger et al. 2006; Ludwig et al. 2007), so where there is a clinical suspicion of pheochromocytoma, a detailed family history and clinical examination for the physical characteristics of the following familial/genetic syndromes should be undertaken.

Neurofibromatosis type 1 (NF-1) – Café au lait patches, axillary freckling, neurofibromas, macrocephaly, and Lisch nodules of iris

Multiple endocrine neoplasia type 2B (MEN2B) – Marfanoid habitus, ganglioneuromatosis of bowel, neuromas of tongue and lips, hyperplasia of nerves of conjunctiva

Multiple endocrine neoplasia type 2A (MEN 2A) – Thyroid mass, Hirschsprung's disease, cutaneous lichen amyloidosis

Von Hippel–Lindau (VHL) – Retinal hemangiomas, CNS hemangioblastoma (mainly cerebellar), renal carcinoma (usually in adult life)

Paraganglioma syndrome (SDH) – Head and neck paragangliomas, intra-adrenal paragangliomas, extra-adrenal paragangliomas

42.1.3 Diagnostic Investigations

42.1.3.1 Biochemical

The diagnosis of pheochromocytoma should be confirmed by the measurement of at least two 24-h

urine samples for metanephrines (normetanephrine or metanephrine) and catecholamines, and the degradation product urinary vanillylmandelic acid (VMA) (Lenders et al. 2002; Pacak et al. 2007). If the diagnosis of pheochromocytoma is in doubt, for superior diagnostic accuracy, measurement of plasma-free metanephrine and normetanephrine are considered more accurate biochemical tests both in adults and probably in children (Sawka et al. 2003; Weise et al. 2002).

42.1.3.2 Imaging/Localizing Investigations

Tumor localizing investigations should not be performed until a biochemical diagnosis has been made. However, where there is a hereditary or genetic predisposition, imaging investigations may be used for screening. Magnetic resonance imaging (MRI) of the abdomen and pelvis should be performed avoiding the radiation exposure of computed tomography (CT) scan. The MRI scan clearly helps to localize site of the tumor, assess its size, and look at its relationships to major vessels (Pacak et al. 2001). Functional imaging is required, however, using I^{123} metaiodobenzylguanidine (MIBG) scintigraphy to confirm the diagnosis and detect multiple synchronous primaries and possible malignant disease (Ilias and Pacak 2004; Velchik et al. 1989). This may necessitate further cross-sectional imaging. It should be noted that malignant paragangliomas lose the ability to accumulate MIBG and hence may not detect all sites of metastatic disease. Further imaging that may be useful in this situation include [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) (Timmers et al. 2007a).

42.1.3.3 Other Investigations

Echocardiography and ECG for long-standing evidence of hypertension.

42.1.4 Preoperative Medical Management

Definitive treatment for pheochromocytoma is surgical resection but only after there has been effective blockade of catecholamines for at least 10–14 days prior to surgery. If there is adequate preoperative α-adrenergic blockade with phenoxybenzamine, as the usual agent, the risk of intraoperative complications is significantly reduced (Goldstein et al. 1999). Doxazosin could be considered if phenoxybenzamine is poorly tolerated. β blockers for tachycardia should only be used after adequate α-adrenergic blockade has been achieved. Adequate hydration is necessary to support the relatively reduced circulating blood volume resulting from the α-blockade (Hack 2000).

42.1.5 Operative Management

The preferred approach to resection is laparoscopic, but open resection is acceptable, particularly with invasive or metastatic disease (Brunt et al. 2002). If there are multiple tumors, there should be an attempt to remove all tumors at the same time, and in children with bilateral adrenal involvement, cortical-sparing adrenalectomies should be considered to avoid the difficulties of cortical steroid replacement during adolescence (Table 42.1.3).

42.1.6 Malignant Paragangliomas

The incidence of malignancy is probably low at less than 6% in childhood paragangliomas (Barontini et al. 2006; Chrisoulidou et al. 2007; Criftci et al. 2001). Malignancy cannot be diagnosed by histology alone but by the presence of local invasion and/or metastatic disease usually in bone, lung, or liver. Although generally incurable, some patients can survive for many years (Havekes et al. 2007). There is little or no literature on children with malignant paragangliomas, but individual cases are included in adult series (Gonias et al. 2009; Havekes et al. 2007). Unresectable tumors can be managed symptomatically in order to improve the quality of life of the child with either phenoxybenzamine or doxazosin. Following debulking surgery, MIBG therapy maybe effective either alone or in association with chemotherapy (Sisson et al. 1999) (Loh et al 1997) usually a combination of vincristine, cyclophosphamide, and dacarbazine (Auerbach et al. 1988). In a recent study, including small numbers of children, high-dose MIBG therapy was used with stem cell support producing an improved 5 year survival rate of 64% but with significant toxicities (Gonias et al. 2009).

Temozolamide may have a role presurgery in reducing metastatic disease, although this is based only on a single case report (Bravo et al. 2009).

Table 42.1.3 Guidelines for diagnosis and management of pheocromocytoma and paraganglioma

Physical examination	Hypertension, mass in abdomen or in neck, signs of familial/genetic syndromes such as neurofibromatosis type 1, MEN 2A, or B
Laboratory assessment	24-h urine samples for metanephrines (normetanephrine or metanephrine) and catecholamines
Radiological assessment	
– First assessment	Ultrasound if abdominal mass
– Local staging	Magnetic resonance imaging (MRI) of the primary site is mandatory for local extension assessment before any treatment. MRI avoids exposure to radiation in patients predisposed to further malignancies
– Diagnostic work	I^{123} metaiodobenzylguanidine (MIBG) scintigraphy to confirm the diagnosis and to detect multiple synchronous primaries and possible malignant disease
Pathological assessment	BIOPSY SHOULD NOT BE ATTEMPTED The tumor should be completely resected providing enough diagnostic material for immunochemistry, cytogenetics, biological studies, and central pathology review
General treatment guidelines	Need for multidisciplinary approach
– Surgery	Keystone of treatment Goal: Complete resection and should be referred to specialist centers The preferred approach to resection is laparoscopic, but open resection is acceptable, particularly with invasive or metastatic disease. If there are multiple tumors, there should be an attempt to remove all tumors at the same time, and in children with bilateral adrenal involvement, cortical-sparing adrenalectomies should be considered to avoid the difficulties of cortical steroid replacement during adolescence
– Radiotherapy	No role in the management of paragangliomas. MIBG therapy may be useful in malignant disease with metastases for palliation of symptoms
– Chemotherapy	No role for chemotherapy except in malignant disease with metastases usually following MIBG therapy with a combination of vincristine, cyclophosphamide, and dacarbazine

42.1.7 Carotid Body Tumors

Carotid body tumors (CBT) are a distinct clinical group of extra-adrenal paragangliomas which arise in the chemoreceptive tissue located in the carotid bifurcation or glomus body and hence also described as glomus body tumors. Certainly, in adults, CBT is the most frequent paranganglioma in the head and neck (Dardik et al. 2002; Pellitteri et al. 2004); however, data in children is lacking with only individual cases reported (Gounot et al. 1990; Ophir 1991) either in adults series, (Dickinson et al. 1986; Shamblin et al. 1971) or in pediatric paraganglioma series (Takautz et al. 2003). Carotid body tumors are often bilateral (Dardik et al. 2002; Dickinson et al. 1986), can be multicentric, the most common association between an intravagal paraganglioma and CBTs (Borba and Al-Mefty 1996). Carotid body tumors are usually sporadic but rarely can have a familial inheritance associated with paraganglioma syndromes due to mutations in the succinate dehydrogenase (SDH) genes (Benn et al. 2006). Presentation is usually as a slowly enlarging pulsatile mass in the upper neck, often misdiagnosed as cervical lymphadenopathy, neurofibromas, or brachial cysts. Later, cranial nerve or adjacent pharynx may be involved (Gujrathi and Donald 2005; Takautz et al. 2003).

Malignancy is rare in CBTs (Shamblin et al. 1971), and as with paragangliomas arising at other sites, it is defined by metastatic spread, usually to cervical lymph nodes but infrequently to distant organs. The risk of malignancy is probably greatest in younger patients with heritable tumors associated with SDH mutations (Timmers et al. 2007b). There is only one report, however, of a child with distant metastatic disease from a CBT (Hajnzic et al. 1999).

Once CBTs are suspected, ultrasound studies can help exclude other causes of neck masses such as lymph nodes, thyroid, or brachial cysts with Doppler studies evaluating the hypervascularity of the tumor. MRI scanning, however, usually reveals a well-defined carotid space lesion (Mey et al. 2001). ^{111}In octreotide scintigraphy can detect metastases in patients with malignant tumors with a role for possible PET scanning (Gujrathi and Donald 2005). Complete surgical resection is usually curative for the majority of patients with prior tumor embolization only being reported in one child (Zaupa and Höllwarth 2007),

although there is still a risk of stroke or cranial nerve palsies. Larger and more invasive CBTs in children may require carotid shunting and vascular reconstruction (Thompson and Cohen 1989). The treatment of malignant CBTs remains, as for other paragangliomas, surgical, though as nonsecreting tumors, they do not respond to α-adrenergic blockade with phenoxybenzamine.

42.1.8 Genetic Management

Following the diagnosis of paranganglioma in childhood, referral for genetic testing should be done in all cases as approximately nearly half of paranganglioma in children will have an underlying genetic or hereditary basis (Krijger et al. 2006). The absence of a family history does not preclude the patient having a mutation; indeed childhood paragangliomas can be considered a probable genetic disease requiring lifelong follow-up (Ein et al. 1990). It is important when taking a history and examining patients with paragangliomas to consider a diagnosis of the following hereditary syndromes.

42.1.8.1 Multiple Endocrine Neoplasia Type 2 (MEN 2)

This autosomal dominant tumor syndrome is a result of a mutation in the *RET* (rearranged during transfection) proto-oncogene in an autosomal dominant pattern. There is a high percentage of bilateral paranganglioma in more than 50% of cases, but malignant paragangliomas are rare (Eisenhofer et al. 2001).

42.1.8.2 Von Hippel–Lindau (VHL) Disease

This autosomal dominant disease is due to a mutation in the *VHL* gene on chromosome 3p25-26 with paragangliomas developing in 10–20% of patients (Ong et al. 2007). Though the paragangliomas mainly develop in adulthood, they have been reported in children with VHL and are often bilateral, but malignant disease is rare (Criftci et al. 2001; Krijger et al. 2006; Ludwig et al. 2007).

42.1.8.3 Neurofibromatosis Type 1 (NF 1)

This distinctive clinical syndrome occurs from a mutation in the *NF1* gene on chromosome 17q11.2. Paragangliomas only occur in a small percentage of patients.

42.1.8.4 Paraganglioma Syndrome (SDH)

Mutations in subunits of the succinic dehydrogenase enzyme complex gene in the mitochondrial respiratory chain are associated with familial paragangliomas. Two particular subunits, SDH and SDHB, are most likely to be associated with childhood with paragangliomas (Pham et al. 2006). Patients with SDHD mutation are more likely to have head and neck paranganglioma, multifocal disease, and a small chance of developing malignant tumors (Benn et al. 2006; Havekes et al. 2007). Patients with SDHB mutations are more likely to present at a younger age with paragangliomas in extra-adrenal sites with a higher chance of metastatic disease (Benn et al. 2006; Ludwig et al. 2007; Timmers et al. 2007b).

42.1.9 Conclusions

The management and diagnosis of paragangliomas in childhood has improved over time with better preparation prior to surgery, increasing use of laparoscopic techniques, and potentially newer imaging studies to detect metastatic disease. The outcome is generally excellent for children, but genetic testing is paramount to determine the lifelong risk for further disease and malignancy.

42.2 Adrenocortical Tumors in Children

Carlos Rodriguez-Galindo

42.2.1 Introduction

Adrenocortical tumors (ACT) encompass a spectrum of diseases with often seamless transition from benign (adenoma) to malignant (carcinoma) behavior. Their incidence in children is extremely low (only 0.2% of pediatric cancers) (Bernstein and Gurney 1999), and most pediatric oncologists see few cases or none. Little is known about these tumors, and most available information has been learned from their more frequent adult counterpart. In recent years, an international registry has provided insight into the clinical characteristics and relevant management issues regarding pediatric ACT and tumor tissue for biological studies. These studies have resulted in the discovery of a novel mechanism of tumorigenesis (Ribeiro et al. 2001).

42.2.2 Epidemiology of Adrenocortical Cancer

ACT appear to follow a bimodal distribution, with peaks during the first and fourth decades (Wooten and King 1993). In children, 25 new cases are expected to occur annually in the United States, for an estimated annual incidence of 0.2–0.3 cases/million. Internationally, however, the incidence of ACT appears to vary substantially. The incidence of ACT is particularly high in southern Brazil, where it is approximately 10–15 times of that observed in the United States. Most cases occur in the contiguous states of Sao Paulo, Paraná, and Santa Catarina (Figueiredo et al. 2006; Pianovski et al. 2006; Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005).

Predisposing genetic factors have been implicated in >50% of the cases in North America and Europe and in 95% of the Brazilian cases. Germline *TP53* mutations are almost always the predisposing factors. In the non-Brazilian cases, relatives of children with ACT often, though not invariably, have a high incidence of other nonadrenal cancers (Li–Fraumeni syndrome), and germline mutations usually occur within the region coding for the *TP53* DNA-binding domain (exons 5–8, primarily at highly conserved amino acid residues). In the Brazilian cases, in contrast, the patients' families do not exhibit a high incidence of cancer, and a single, unique mutation at codon 337 in exon 10 of the *TP53* gene is consistently observed (see below).

Patients with Beckwith–Wiedemann and hemihypertrophy syndromes have a predisposition to cancer, and as many as 16% of their neoplasms are ACT (Hoyme et al. 1998). However, less than 1% of children with ACT have these syndromes (Steenman et al. 2000). ACT have also been reported in association with other genetic diseases such as congenital adrenal hyperplasia (Varan et al. 2000).

The differential diagnosis of ACT includes other diseases characterized by adrenal hormone hyperproduction. ACTH-independent macronodular adrenal hyperplasia (AIMAH) is a benign proliferative disorder of the adrenal cortex that presents with ACTH-independent Cushing's syndrome. The majority of patients with AIMAH present in the fifth decade of life with sporadic isolated disease; however, in children, AIMAH can be associated with McCune–Albright syndrome (Sutter and Grimberg 2006). A similar macronodular adrenocortical hyperplasia is seen in up to one third of patients with multiple endocrine neoplasia syndrome type 1 (MEN1) and although rare, adrenocortical carcinomas have been described in this population, usually in adult age (Langer et al. 2002). Primary pigmented nodular adrenocortical disease (PPNAD) is a benign bilateral proliferative disorder characterized by small hyperpigmented nodules, usually associated with the Carney complex. This is an autosomal dominant syndrome that includes lentiginosis (perioral, ocular, or genital), cardiac and peripheral myxomas, melanotic schwannomas, and endocrine overactivity. Clinically evident PPNAD is seen in up to 30% of patients with Carney complex and usually presents in childhood, late adolescence, or early adulthood (Sutter and Grimberg 2006).

42.2.3 Biology of ACT

The molecular mechanisms of tumorigenesis of the adrenal cortex are not well understood (Kirschner 2002; Barlaskar and Hammer 2007). Carcinogenesis is a multistep process, and the pathogenesis of ACT may combine dedifferentiation and unchecked proliferation

induced through the activation of hormonal or growth factor signaling receptors. The insulin-like growth factor (IGF) system is well characterized for its contribution to normal and pathological adrenocortical growth. Clues to the role of this pathway in the development of ACT also came through the recognition of the increased incidence of ACT in children with Beckwith–Wiedemann syndrome (BWS) (Steenman et al. 2000). Genetic alterations associated with BWS are mapped to regions of chromosome band 11p15 designated BWS chromosomal regions (*BWSCR*) 1, 2, and 3 (Steenman et al. 2000). *IGF2* is mapped to *BWSCR1*. The strong association of BWS, *IGF2*, and ACC suggests that IGF2 participates in tumorigenesis, and studies have shown increased IGF2 protein and mRNA in ACC (Ilvesmaki et al. 1993; Boulle et al. 1998). Sporadic adrenocortical carcinomas (ACC) also show striking overexpression of *IGF2*, and studies in adults have documented >100-fold higher expression levels in carcinomas in comparison to adenomas and normal adrenal tissue (Gicquel et al. 2001). This differential *IGF2* expression between adenomas and carcinomas doesn't seem to be observed in pediatric tumors (see below) (Almeida et al. 2008; West et al. 2007). Interestingly, the antiproliferative effect of ACTH is blunted in ACT cell lines overexpressing *IGF1R* (Weber et al. 2000). Further, transgenic mice expressing *IGF2* postnatally develop adrenal hyperplasia (although not frank malignancy) (Weber et al. 1999). Taken together, the evidence strongly suggests that the IGF system is involved in adrenal growth and tumorigenesis. High local IGF2 levels combined with elevated *IGF1R* expression would provide a significant growth advantage, but additional steps are required for neoplastic transformation (Kirschner 2002; Barlaskar and Hammer 2007; Weber et al. 2000). Studies in several model organisms indicate the presence of undifferentiated multipotent adrenocortical cells, and a few molecular studies have implicated Wnt signaling pathway activation in ACC (Tissier et al. 2005). Further investigations are necessary to elucidate the contributions of developmental signaling pathways like Wnt in adrenal tumorigenesis.

The hypothetical multistep transformation process also requires intracellular signaling abnormalities other than dedifferentiation- and proliferation-inducing signals. *TP53* mutations appear to underlie such abnormalities in most cases, and ACT are strongly associated with germline *TP53* mutations. ACT are among the tumors most increased in frequency in families with Li–Fraumeni syndrome (Birch et al. 2001; Kleihues et al. 1997; Gonzalez et al. 2009), suggesting that germline *TP53* mutations exert tissue-specific effects. The diagnosis of ACT in a young patient should be considered a strong indicator of a germline *TP53* mutation, regardless of the family history (Gonzalez et al. 2009). A wide spectrum of germline *TP53* alterations have been described in ACT, and these mutations may contribute to the etiology of more than 80% of cases in children (Varley et al. 1999; Wagner et al. 1994). Consistent with the presence of a germline *TP53* mutation, relatives of children with ACT often have a high incidence of cancer; however, the lack of family history should not preclude investigation of *TP53* germline status (Varley et al. 1999; Wagner et al. 1994; Ariffin et al. 2008; Khayat and Johnston 2004; Rossbach et al. 2008). In North American children, the spectrum of germline *TP53* mutations in ACT is quite diverse, although germline mutations occur primarily in the *TP53* DNA-binding domains (exons 4–8) (Wagner et al. 1994; Reincke et al. 1994; Varley et al. 1999). In the Brazilian cases, by contrast, the patients' families do not have a high incidence of cancer, and a single mutation in exon 10 of the *TP53* gene is consistently observed. This mutation encodes an arginine in place of histidine at codon 337 (*TP53*-R337H) within the tetramerization domain. The families of these children do not share common ancestry. Recent studies have indicated that the R337H mutation is a relatively common polymorphism among southern Brazilians. Further, the penetrance of this mutation is low (only 10–15% of carriers develop ACT), and it appears not to predispose carriers to other malignancies later in life (Figueiredo et al. 2006). The wild-type allele is deleted in these tumors, and the mutant p53 protein accumulates in the nucleus. Functional analyses have shown that the mutant TP53 retains transactivation function and can induce apoptosis (Ribeiro et al. 2001). However, the mutant tetramerization domain is less stable than the wild-type domain and is sensitive to slightly increased pH, suggesting that a unique physiological condition within adrenocortical cells may contribute to the observed tissue-restricted pathogenesis (DiGiammarino et al. 2001). Thus, this inherited unique *TP53* mutation represents a low-penetrant, hypomorphic allele that contributes to the development of ACT in a tissue-specific manner (Ribeiro et al. 2001). Other *TP53* mutations, such as

the *TP53*R157L, with sufficient activity to suppress Li–Fraumeni syndrome but not ACC, have been described (West et al. 2006), thus the importance of in-depth evaluation and genetic counseling of children with ACT and their families.

Additional genetic alterations may be necessary for malignant transformation. ACT are characterized by a high frequency of chromosomal gains and amplifications, and several chromosomal subregions containing candidate proto-oncogenes are affected (Dohna et al. 2000; Figueiredo et al. 1999; Loncarevic et al. 2008). Interestingly, the pattern of genomic imbalances in pediatric ACT appears to be different from their adult counterparts. In a series of nine cases in Southern Brazil, the most consistent findings were a gain of all or part of chromosome arm 9q (eight cases) and amplification of band 9q34 (five cases) (Figueiredo et al. 1999). Loncarevic et al. analyzed 14 pediatric ACT by comparative genomic hybridization. Recurring genomic changes included gains of 1q, 12p, 12q, 1p, 7q, 9q, and 15q; and losses of 4q, 11q, 4p, and 16q (Loncarevic et al. 2008). Of particular interest is the consistent finding of gain of 9q in both series. The steroidogenic factor 1 gene (*SF1*, *NR5A1*) is located within this region and has been shown to be overexpressed in nearly all childhood ACT (Doghman et al. 2007). Enforced expression of *SF1* increases human adrenocortical cell proliferation and promotes adrenocortical tumorigenesis in transgenic mouse models. Collectively, these findings strongly implicate *SF1* as a driver in the initiation and/or progression of ACT. Additional studies are required to determine whether deregulation of *SF1* cooperates with *TP53* loss in ACT.

Microarray studies in childhood ACT show distinct patterns of gene expression that distinguish normal adrenal tissue, adenomas, and carcinomas (West et al. 2007). A significantly increased expression of *FGFR4* and *IGF2* was found in childhood ACC, although the degree of *IGF2* expression seems to be lower than adult tumors, and in contrast to adult ACT, this expression does not distinguish childhood adrenocortical adenoma from carcinoma. Also, there was a remarkable correlation in gene expression profiles between normal fetal adrenal tissue and pediatric ACT. There were very significant differences in gene expression between pediatric adenomas and carcinomas; remarkably, expression of major histocompatibility class II genes was lower in carcinomas than in adenomas, suggesting that malignant tumors may have evolved mechanisms to evade recognition by the immune system (West et al. 2007).

The distinctive clinical features suggest that ACT arises from the fetal zone of the fetal adrenal cortex. The fetal zone represents 85% of the adrenal cortex during fetal development, and it is oriented toward dehydroepiandrosterone production. It is thus possible that the presence of a constitutional *TP53* mutation increases the penetrance of ACT in the fetal adrenal cortex with lower risk for the remaining layers. Disruption of the *TP53* pathway under certain conditions may result in abnormalities of other cellular pathways leading to tumor formation.

42.2.4 Clinical Characteristics of Pediatric ACT

The clinical characteristics, treatment, and outcome of ACT have been described mainly in adults; because there are few reports about pediatric ACT, it is difficult to discriminate features unique to either age group. The degree and type of endocrine disturbance appear to be related to patient age (Wooten and King 1993; Wajchenberg et al. 2000). Older patients tend to have a much higher incidence of nonfunctional tumors, whereas more than 90% of childhood ACT are functional (Wajchenberg et al. 2000; Ribeiro et al. 1990; Ciftci et al. 2001; Driver et al. 1998). Adults usually have mixed virilization-hypercortisolism syndromes, whereas virilization syndrome is the most common presentation in children (Wajchenberg et al. 2000; Ribeiro et al. 1990; Ciftci et al. 2001; Driver et al. 1998).

Despite the rarity of childhood ACT, its clinical and pathologic characteristics have been well characterized in recent years (Ribeiro et al. 1990; Ciftci et al. 2001; Driver et al. 1998; Wieneke et al. 2003; Sandrini et al. 1997; Bugg et al. 1994; Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005; Teinturier et al. 1999). Significant information has been obtained from the International Pediatric Adrenocortical Tumor Registry (IPACTR) (www.stjude.org/ipactr), established in 1990 by the St. Jude Children's Research Hospital International Outreach Program, and institutions in Brazil. The registry has served as an information-exchange Web site, and more than 300 patients have been registered to date (Michalkiewicz et al. 2004). The registry now also includes a tumor bank component to collect from international sites both

normal and adrenal tumor tissue for detailed biological studies.

Childhood ACT typically present during the first 5 years of life (median age, 3–4 years), although there is a second, smaller peak during adolescence (Ribeiro et al. 1990; Ciftci et al. 2001; Wieneke et al. 2003; Sandrini et al. 1997; Teinturier et al. 1999; Michalkiewicz et al. 2004; Narasimhan et al. 2003). Female sex is consistently predominant in most studies, with a female to male ratio of 1.6:1 (Wieneke et al. 2003; Sandrini et al. 1997; Michalkiewicz et al. 2004; Ciftci et al. 2001; Narasimhan et al. 2003; Hanna et al. 2008). According to the IPACTR data, the female predominance is more significant for patients younger than 3 years of age (1.7:1) and for patients older than 13 years (6.2:1), but not for patients between 3 and 12 years (Michalkiewicz et al. 2004). Because pediatric ACT are almost universally functional, they cause endocrine disturbances, and a diagnosis is usually made 5–8 months after the first signs and symptoms emerge (Ciftci et al. 2001; Wieneke et al. 2003; Michalkiewicz et al. 2004). Virilization (pubic hair, accelerated growth, enlarged penis, clitoromegaly, hirsutism, and acne) due to excess of androgen secretion is seen, alone or in combination with hypercortisolism, in more than 80% of patients (Fig. 42.2.1). Isolated Cushing's syndrome is very rare (5% of patients), and it appears to occur more frequently in older children (median age 12.6 years in the IPACTR) (Ciftci et al. 2001; Wieneke et al. 2003; Teinturier et al. 1999; Michalkiewicz et al. 2004; Hanna et al. 2008).

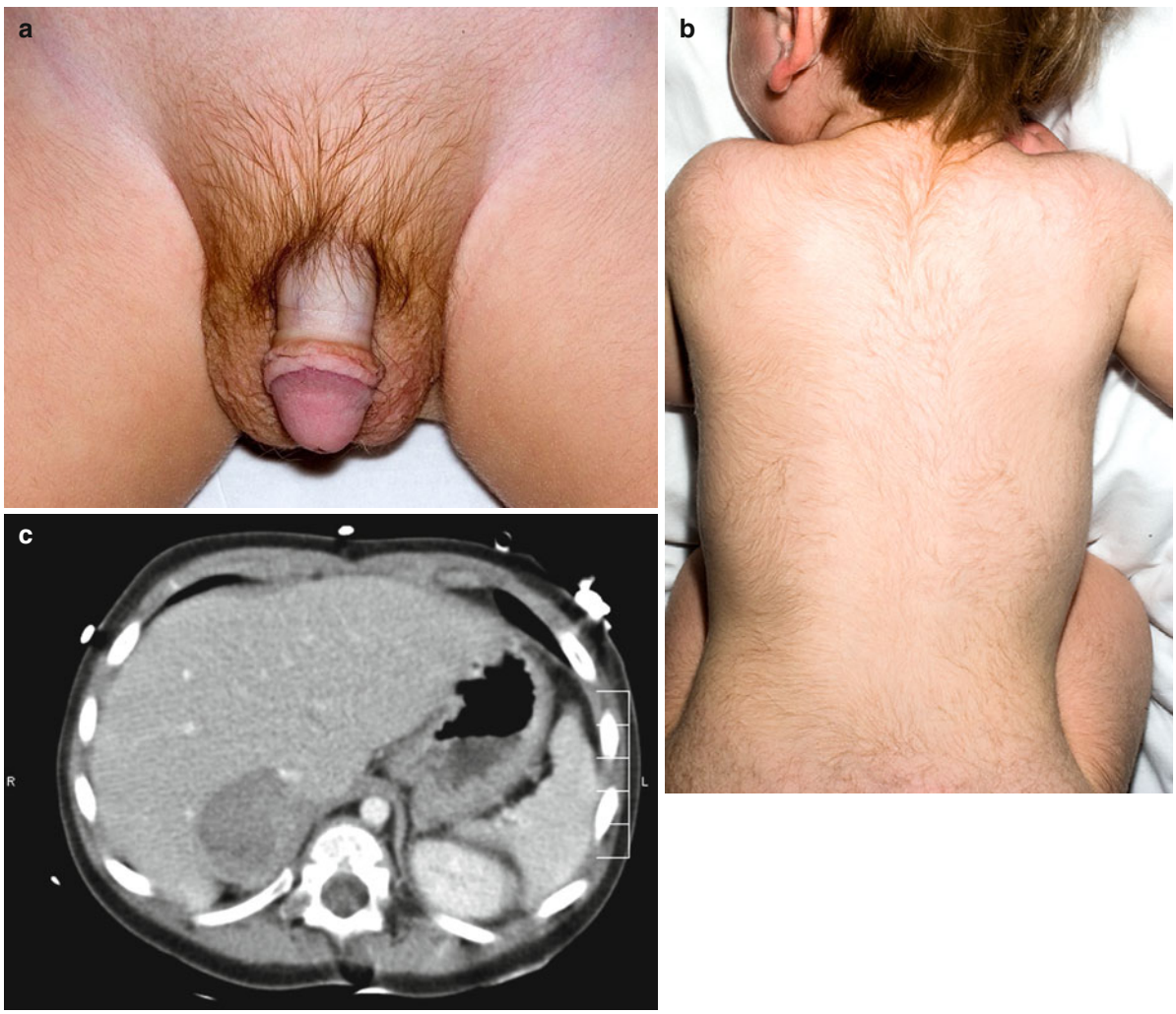

Fig. 42.2.1 Two-year-old boy presenting with virilization (**a**, **b**). CT scan demonstrated a right adrenal mass (**c**)

Likewise, nonfunctional tumors are rare (less than 10%) and tend to occur in older children (Michalkiewicz et al. 2004). Half of the patients have severe hypertension at presentation, and hypertensive crisis resulting in seizures is the presenting feature in 10% of cases (Ribeiro et al. 1990; Wieneke et al. 2003; Sandrini et al. 1997; Michalkiewicz et al. 2004; Wang et al. 2007). However, isolated Conn's syndrome with hypertension, hypokalemia, and pseudoparalysis resulting from hyperproduction of aldosterone or deoxycorticosterone is extremely rare (less than 1% in the IPACTR data) but has been described (Michalkiewicz et al. 2004; Narasimhan et al. 2003). An abdominal mass can be palpated in approximately half the patients (Ciftci et al. 2001; Teinturier et al. 1999).

At the time of diagnosis, two thirds of pediatric patients have limited disease (tumors are completely resected), and the remaining patients have either unresectable or metastatic disease (Michalkiewicz et al. 2004). In up to 20% of the cases, intracaval extension of the tumor is present (Michalkiewicz et al. 2004; Tucci et al. 2005). Unlike adult ACT, histologic differentiation of adenomas and carcinomas is difficult. However, approximately 10–20% of pediatric cases are adenomas (Wieneke et al. 2003; Michalkiewicz et al. 2004).

42.2.5 Diagnosis

Children with ACT usually present with striking endocrine syndromes, most commonly virilization, and thus are usually diagnosed earlier than adults. Because of the hormone hypersecretion, it is possible to establish an endocrine profile for each particular tumor, which may facilitate the evaluation of response to treatment and monitor for tumor recurrence. Laboratory evaluation can also help distinguish physiological adrenarche or congenital adrenal hyperplasia from ACC. Patients with adrenarche have elevated basal concentration of DHEAS and androstenedione, while those with congenital adrenal hyperplasia may show increased basal or ACTH-stimulated peak concentration of 17-OH-progesterone (Ribeiro and Figueiredo 2004). While the diagnosis of ACC is usually clinical, imaging studies are important to complete staging and for surgical planning. Magnetic resonance imaging (MRI) and computed tomography (CT) are needed for evaluation of the size and location of the primary tumor, the degree of invasion to surrounding structures, the presence of metastases, and involvement of venous structures. Although bone metastases at diagnosis are extremely rare, scintigraphic studies are recommended. On CT, large tumors usually have a central area of stellate appearance caused by hemorrhage, necrosis, and fibrosis; this central area is usually hyperintense on T2-weighted MRI and STIR images. Calcifications are also common (Ribeiro et al. 2000). In order to evaluate tumor extension into the vena cava, ultrasound or MRI are always recommended, and a careful evaluation of the presence of a tumor thrombus must always be performed prior to surgery (Ribeiro and Figueiredo 2004; Tucci et al. 2005). Because ACT are metabolically active, whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET) is being increasingly used. Although the experience in pediatrics is limited, available information suggests that this may be a very useful technique in the imaging of the regional and metastatic extension, and in the diagnosis of recurrences in areas not typically imaged (Mackie et al. 2006; Murphy et al. 2008).

The distinction between benign (adenomas) and malignant (carcinomas) tumors can be problematic. In fact, adenoma and carcinoma appear to share multiple genetic aberrations and may represent points on a continuum of cellular transformation (Dohna et al. 2000; Figueiredo et al. 1999). Macroscopically, adenomas tend to be well defined and spherical, and they never invade surrounding structures. They are typically small (usually <200 cm^3), and some studies have included size as a criterion for adenoma. Microscopically, they may resemble normal adrenal cortex. By contrast, carcinomas have macroscopic features suggestive of malignancy; they are larger, and they show marked lobulation with extensive areas of hemorrhage and necrosis. Microscopically, carcinomas comprise larger cells with eosinophilic cytoplasm, arranged in alveolar clusters. Several authors have proposed histologic criteria that may help to distinguish the two types of neoplasm (Weiss 1984; Slooten et al. 1985). However, morphologic criteria may not allow reliable distinction of benign and malignant ACC. Mitotic rate is consistently reported as the most important determinant of aggressive behavior (Weiss et al. 1989; Kendrick et al. 2001; Stojadinovic et al. 2002; Harrison et al. 1999). *IGF*2 expression also appears to discriminate between carcinomas and adenomas in adults but not in children (Almeida et al. 2008; West et al. 2007; Rosati et al. 2008; Erickson et al. 2001). Other histopathologic

variables are also important, and risk groups may be identified on the basis of a score derived from characteristics, such as venous, capsular, or adjacent organ invasion; tumor necrosis; mitotic rate; and the presence of atypical mitoses (Stojadinovic et al. 2002). Two retrospective studies have investigated histological criteria of malignancy in pediatric ACT. Bugg et al. analyzed histology, ploidy, proliferative index, and tumor size in 54 cases (Bugg et al. 1994). The histologic criteria for malignant tumors were the mitotic index, the presence of confluent necrosis and atypical mitoses, and the nuclear grade, as previously defined by Weiss (Weiss 1984; Weiss et al. 1989). The most statistically significant predictors of outcome were tumor histology and tumor weight (<100 g vs. >100 g). Ploidy and proliferative index were not predictive of outcome (Bugg et al. 1994). More recently, Wienecke et al. analyzed features associated with increased probability of a malignant behavior in a series of 83 pediatric ACC (Wieneke et al. 2003). Tumor weight >400 g, tumor size >10.5 cm in the largest diameter, vena cava, capsular or vascular invasion, extension into periadrenal soft tissues, confluent necrosis, presence of severe nuclear atypia, atypical mitoses, and presence of >15 mitotic figures/20 high-power field were all associated with adverse outcome. However, on multivariate analysis, only vena cava invasion, presence of necrosis, and high mitotic rate retained prognostic significance. The incorporation of gene expression techniques to the diagnostic evaluation of ACT may provide additional means to anticipate the clinical and biological behavior, both in adult (Reynies et al. 2009) and pediatric (West et al. 2007) tumors. However, still unknown biological events rather than histopathologic tumor characteristics are likely to dictate clinical behavior.

42.2.6 Prognostic Factors

In an analysis of 40 cases in Southern Brazil, Ribeiro et al. (1990) found tumor volume >200 mL or weight >80 g, and age >3.5 years to be associated with worse outcome, although only tumor size was independently predictive. In the IPACTR data, several clinical features, including age, sex, clinical syndrome, interval between first symptoms and diagnosis, blood pressure, disease stage, tumor spillage, tumor thrombus, and tumor weight were examined for their association with outcome. In patients with localized disease, age between 0 and 3 years, virilization alone, normal blood pressure, disease stage I, absence of spillage during surgery, and tumor weight ≤200 g were associated with a greater probability of survival. In a Cox regression model analysis, only stage I, virilization alone, and age 0–3 years were independently associated with a better outcome (Michalkiewicz et al. 2004) (Figs. 42.2.2 and 42.2.3).

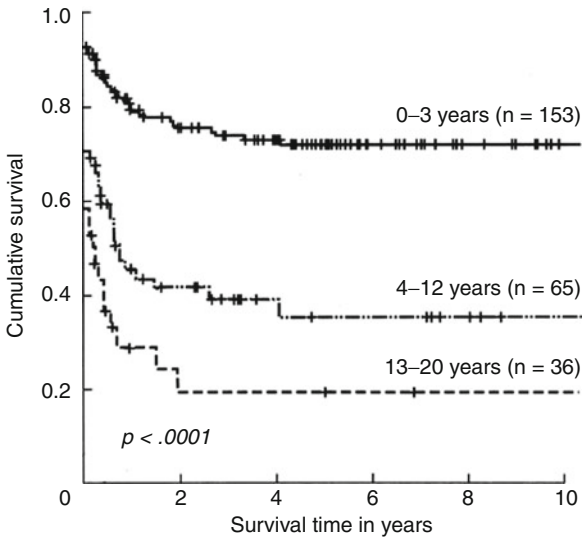

Fig. 42.2.2 Probability of 5-year event-free survival according to age at the time of diagnosis in 254 children with ACT (From Michalkiewicz et al. (2004) With permission)

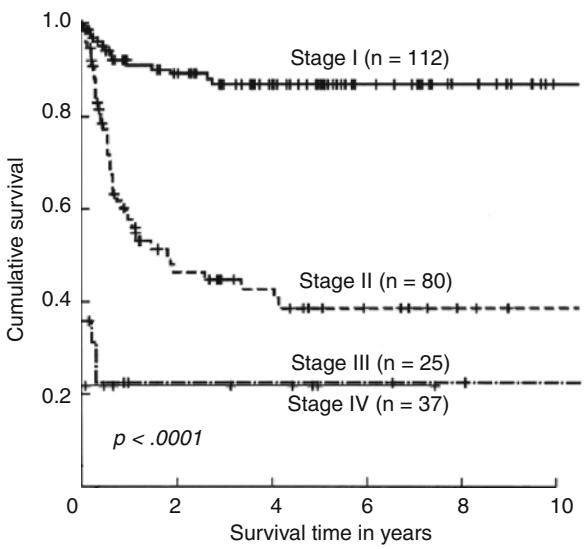

Fig. 42.2.3 Probability of 5-year event-free survival according to disease stage at the time of diagnosis in 254 children with ACT (From Michalkiewicz et al. (2004) With permission)

Table 42.2.1 Proposed staging of adrenocortical tumors in children

- *Stage I*
  - Completely resected, small tumors (<100 g and <200 cm^3) with normal postoperative hormone levels
- *Stage II*
  - Completely resected, large tumors (≥100 g or ≥200 cm^3) with normal postoperative hormone levels
- *Stage III*
  - Unresectable, gross, or microscopic residual disease
  - Tumor spillage
  - Patients with stage I and II tumors who fail to normalize hormone levels after surgery
  - Patients with retroperitoneal lymph node involvement
- *Stage IV*
  - Presence of distant metastases

Modified from Sandrini et al. (1997)

Thus, available data suggest that tumor size is especially important in children; patients with small tumors have an excellent outcome with surgery alone, regardless of histologic features (Ribeiro et al. 1990; Wieneke et al. 2003; Bugg et al. 1994; Michalkiewicz et al. 2004; Michalkiewicz et al. 1997). A staging system based on disease extent and tumor size has been proposed on the basis of these findings (Table 42.2.1) (Rodriguez-Galindo et al. 2005; Sandrini et al. 1997). The overall probability of 5-year survival for children with ACT is reported to be 54–74% (Ciftci et al. 2001; Wieneke et al. 2003; Sandrini et al. 1997; Teinturier et al. 1999; Michalkiewicz et al. 2004; Hanna et al. 2008; Tucci et al. 2005). Data from the IPACTR and other series show the staging system to be highly predictive of outcome in children with stage I or stage IV disease: more than 90% of patients with stage I disease, but only 10% of those with stage IV disease, are long-term survivors (Fig. 42.2.3). Determining the prognosis of patients with intermediate-stage disease is much more difficult. Despite presumed complete tumor resection, local recurrence is the most common adverse event in patients with stage II disease (30–50% of cases) (Michalkiewicz et al. 2004; Tucci et al. 2005).

42.2.7 Treatment of Pediatric ACT

Treatment of childhood ACT has evolved from the data derived from the adult studies, and same guidelines are used; surgery is the most important mode of therapy, and mitotane- and cisplatin-based regimens are recommended for patients with advanced disease (Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005; Zancanella et al. 2006; Hovi et al. 2003). An aggressive surgical approach of the primary tumor and all metastatic sites is recommended when feasible (Tucci et al. 2005; Stewart et al. 2004). Because of tumor friability, rupture of the capsule with resultant tumor spillage is frequent (approximately 20% of initial resections and 43% of resections after recurrence) (Sandrini et al. 1997; Michalkiewicz et al. 2004). In fact, spontaneous tumor rupture resulting in acute abdomen as presentation of a pediatric ACT has been described (Leung et al. 2002). When the diagnosis of ACT is suspected, laparotomy and a curative procedure are recommended rather than fine-needle aspiration, to avoid the risk of tumor rupture (Kardar 2001). Laparoscopic resection is associated with a high risk of rupture and peritoneal carcinomatosis; thus, open adrenalectomy remains the standard of care (Gonzalez et al. 2005). The lymph node drainage of the adrenal gland is complex. There is an extensive subserosal network of lymphatic channels around the gland, crossing several levels in different directions inside the fascia and connective tissue involving the adrenal gland. The incidence of lymph node involvement is not known, although some studies report it to be close to 40% in adults (Crucitti et al. 1996; Lee et al. 1995). In children, available data suggests that nodal involvement is present in approximately 30% of the cases (Stewart et al. 2004). Whether ipsilateral retroperitoneal lymph node dissection may improve local control is a matter of debate and a question currently being investigated in the Children's Oncology Group ARAR0332 study (see below).

Chemotherapeutic regimens used for patients with advanced disease have derived from the standard treatments used in adults. A cisplatin-based combination, usually incorporating doxorubicin and etoposide, is most commonly used (Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005; Ciftci et al. 2001; Teinturier et al. 1999; Michalkiewicz et al. 2004; Zancanella et al. 2006). Because of cisplatin's renal dose-limiting toxicity, Ayass and coworkers substituted carboplatin for cisplatin given in combination with etoposide to a 17-month-old boy with ACT that had metastasized to the brain and chest. After complete resection of the primary tumor and eight cycles of etoposide and carboplatin, the metastatic dis-

ease responded completely and the patient survived long-term (Ayass et al. 1991).

Little information is available about the use of mitotane in children, although response rates appear to be similar to those seen in adults (Ribeiro and Figueiredo 2004; Zancanella et al. 2006). There have been several reports of complete responses in children with advanced or metastatic ACT, but these appear to be rare events (Coelho Netto et al. 1963; Ostuni and Roginsky 1975). In a review of 11 children with advanced ACT treated with mitotane and a cisplatin-based chemotherapeutic regimen, measurable responses were seen in seven patients. The mitotane daily dose required for therapeutic levels was around 4 g/m^2, and therapeutic levels were achieved after 4–6 months of therapy (Zancanella et al. 2006). Compliance with daily mitotane administration is a major limitation to therapy in young children; nausea, vomiting, diarrhea, and neurologic alterations are common (Zancanella et al. 2006). Monitoring for neurotoxicity is particularly important in young patients as the use of mitotane has been associated with motor and speech developmental delays (De Leon et al. 2002).

The use of radiotherapy in pediatric ACT has not been consistently investigated. ACT are generally considered to be radioresistant (Wajchenberg et al. 2000). Furthermore, because many children with ACT carry germline *TP53* mutations that predispose to cancer, radiation may increase the incidence of secondary tumors. Driver et al. reported that three of five long-term survivors of pediatric ACT died of secondary sarcoma that arose within the radiation field (Driver et al. 1998). For most patients with metastatic or recurrent disease that is unresponsive to mitotane and chemotherapy, repeated surgical resection is the only alternative. However, given the infiltrative nature of the disease, complete resection is difficult to achieve. Image-guided tumor ablation with radiofrequency currently offers a valid alternative for these patients. Radiofrequency ablation is a minimally invasive and safe treatment for patients in whom surgery may not be possible. Using this technique, Wood et al. reported responses in 53% of the adult patients treated; these results suggest that radiofrequency ablation has a role in the management of this aggressive malignancy (Wood et al. 2003). Data regarding the use of this treatment modality in children is limited; however, it appears to offer a valid alternative for children with unresectable ACT (Hoffer et al. 2009).

Finally, advances in our understanding of ACT biology may lead to the identification of new molecular targets (Kirschner 2006). In particular, new developments in IGF pathway inhibition, such as monoclonal antibodies against the IGF1R, may provide effective alternatives and are currently being investigated (Table 42.4.1) (Almeida et al. 2008; Barlaskar et al. 2009).

42.2.8 A Collaborative Research Initiative for Childhood ACT

Cooperative multi-institutional efforts have been pivotal in the advancement of pediatric oncology during the past several decades. Rare pediatric tumors, however, have remained research orphans, and children with these rare malignancies have yet to benefit from group-wide initiatives. In recent years, the Children's Oncology Group (COG) has made a commitment to develop research programs in rare childhood malignancies. Part of this effort is a collaboration between COG and Brazilian institutions to develop a study protocol for childhood ACC (ARAR0332) (Table 42.2.2). This protocol investigates three main clinical questions: (1) the efficacy of surgery alone for stage I tumors; (2) the role of retroperitoneal lymph node resection in reducing local recurrence of stage II tumors; and (3) the impact of mitotane- and cisplatin-based chemotherapy for unresectable and metastatic disease.

The ARAR0332 protocol also attempts to provide further insight into the biology of ACC and the different patterns of *TP53* mutations. In addition to the near-requisite germline *TP53* mutations, a number of consistent chromosomal gains and losses have been observed in childhood ACT. These genetic alterations

Table 42.2.2 Treatment on the COG ARAR 0332 protocol

Stage	Treatment
Stage I	• Surgery alone
Stage II	• Surgery • RPLN dissection
Stage III	• Mitotane • CDDP/ETO/DOX • Surgery + RPLN dissection
Stage IV	• Mitotane • CDDP/ETO/DOX • Surgery + RPLN dissection

RPLN retroperitoneal lymph node, *CDDP* cisplatin, *ETO* etoposide, *DOX* doxorubicin

Table 42.4.1 Guidelines for diagnosis and management of pediatric adrenocortical tumors

Physical examination	Virilization is a hallmark. Other signs of hormone hyperproduction such as Cushing's syndrome or hypertension are also common. Less frequently, signs of Beckwith–Wiedemann or MEN-I syndromes
Laboratory assessment	High adrenal hormones, primarily DHEA, DEHA-S, and Androstendione; less frequently cortisol, deoxycorticosterone
Radiological assessment	Always try to limit radiation exposure in young children with possible or documented germline *TP53* mutation
– First assessment	Ultrasonogram or computed tomography (CT) of the abdomen
– Local staging	CT or MRI of the abdomen. Important to visualize adrenal veins and inferior vena cava for tumor thrombus, and retroperitoneal structures for nodal metastases (rare). Tumor implants may be present in tumor spillage
– Diagnostic work	CT chest to rule out lung metastases and to visualize superior vena cava for tumor thrombus. PET scan has proven to be helpful in diagnosis and monitoring of recurrence
Pathological assessment	Always avoid needle biopsy due to risk of tumor spillage. Distinction between adenomas and carcinomas often difficult. Size and presence of mitosis, necrosis, and nuclear atypia are associated with adverse outcome
Staging systems for risk-adapted treatment strategy	*Stage I* – Completely resected, small tumors (<100 g and <200 cm^3) with normal postoperative hormone levels *Stage II* – Completely resected, large tumors (≥100 g or ≥200 cm^3) with normal postoperative hormone levels *Stage III* – Unresectable, gross or microscopic residual disease – Tumor spillage – Patients with stage I and II tumors who fail to normalize hormone levels after surgery – Patients with retroperitoneal lymph node involvement *Stage IV* – Presence of distant metastases
General treatment guidelines	Importance of a multidisciplinary approach, with aggressive surgery of primary and metastatic lesions
– Surgery	Keystone of therapy; upfront resection if possible
	Risk of tumor rupture and spillage is high, and therefore, laparoscopic procedures should be avoided
– Radiotherapy	Should be avoided when possible given the high frequency of germline *TP53* mutations in young children with ACT
	Role limited to palliation
– Chemotherapy	For patients with locally advanced and metastatic disease
	Cisplatin-based regimens, usually including etoposide and doxorubicin
	Long-term treatment with mitotane is recommended, but levels must be monitored closely
– Radiofrequency ablation	Helpful in cases of unresectable disease
– Supportive care	Importance of close endocrinologic monitoring; patients on mitotane often develop long-term adrenal insufficiency, hypothyroidism, and other hormonal dysfunctions

presumably favor the expression of tumor-promoting oncogenes while eliminating potential tumor suppressors. Genomic DNA analyses used with microarray gene expression profiling should allow the identification of the genes that cooperate with p53 inactivation to promote development of ACT.

42.3 Medulloepithelioma

Gianni Bisogno

Medulloepithelioma (MEP) is a rare tumor derived from the primitive neuroepithelium located in the ciliary body of the eye; however, tumors arising from the optic nerve or from the central nervous system have also been described (Vajaranant et al. 2005; Molloy et al. 1996).

Ocular medulloepitheliomas occur in early childhood with a mean age at diagnosis of 4 years. Rarely, these tumors can affect adults possibly as a late malignant transformation of a benign asymptomatic MEP arisen in childhood (Carrillo and Streeten 1979). It is a locally aggressive tumor that may extend anteriorly into the iris or posteriorly into the vitreous cavity involving the retina, with the entire globe filled with tumor similar to retinoblastoma. In advanced cases, it may present with extraocular extension and involve the regional lymph nodes. Distant metastasis to lungs and parotid gland have been rarely described (Broughton and Zimmerman 1978; Viswanathan et al. 2008). There is no racial or sexual predilection, and both eyes are equally affected (Vajaranant et al. 2005).

MEP can be associated with central nervous system malignancies (i.e., pinealoblastoma) or malformations (i.e., corpus callosum agenesia, schizencephaly) (Vajaranant et al. 2005). In addition, it has recently been suggested that MEP is a manifestation of a familiar tumor predisposition associated with pleuropulmonary blastoma (Priest et al. 2011).

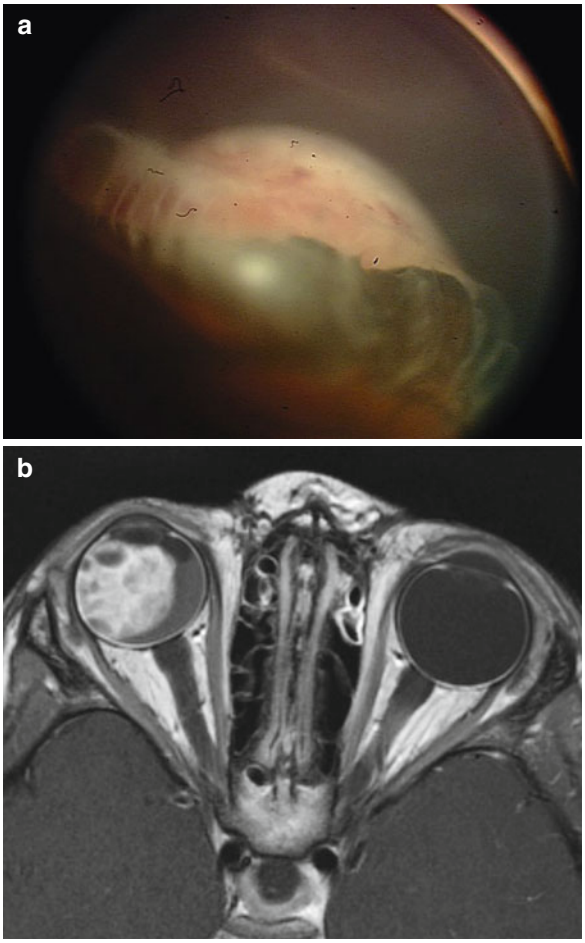

Fig. 42.3.1 (**a**) Medulloepithelioma-Variably pigmented cilliary body mass. (**b**) MRI highlights characteristic intralesional cysts.

42.3.1 Clinical Characteristics

The most common presenting symptoms are pain and poor vision, related to secondary lens subluxation, glaucoma, or cataract formation. Leukocoria and the evidence of a mass in the iris or ciliary body are also part of the initial signs (Chung et al. 2007).

On fundoscopic examination, the tumor presents an irregular surface with characteristic cystic lesions (Fig. 42.3.1a). In up to 60% of patients, cysts break off the surface and float freely in aqueous or vitreous humor. Retinal detachment is seen in many cases. MEP may also contain calcifications in some cases (Chung et al. 2007).

On ultrasound, MEP appears as an echogenic irregular mass with a cystic structure and calcification in some cases. CT scan shows a dense irregular mass in the region of the ciliary body with marked to moderate enhancement after contrast. On MRI, the mass is moderately hyperintense compared to vitreous on T1-weighted images, hypointense on T2-weighted images with marked enhancement after gadolinium administration (Fig. 42.3.1b) (Vajaranant et al. 2005).

42.3.2 Diagnosis

The diagnosis requires a histopathologic examination. MEP is characterized by proliferating sheets and cords of poorly differentiated neuroepithelium with cystic

spaces in between and rosette-like structures visible in some cases. It has been classified as teratoid and nonteratoid types. The nonteratoid MEP medulloepithelioma is a pure proliferation of cells of the medullary epithelium. The teratoid subtype includes also heteroplastic elements, such as cartilage, skeletal muscle, and brain-like tissue, and account for 30–50% of cases. Benign MEPs medulloepitheliomas exist, but more than two third of cases are malignant. The histopathological criteria for malignancy are the presence of poor cellular differentiation, cellular pleomorphism, sarcomatous changes, and invasion of surrounding ocular tissues (Broughton and Zimmerman 1978).

When MEP is very extensive and includes calcification, it may be difficult to distinguish it from an anteriorly located retinoblastoma. Differential diagnosis should also include benign conditions such xanthogranuloma, a cyst of the ciliary body, or the persistence and hyperplasia of the primary vitreous (PHPV) (Vajaranant et al. 2005; Chung et al. 2007).

42.3.3 Treatment

MEP treatment is usually based on the surgical removal of the tumor. Limited procedures can be adopted with small tumors, but enucleation may be necessary in larger lesions and exenteration when there is evidence of extraocular extension. Unfortunately, there is a substantial risk of relapse even after a complete tumor resection. The prognosis is less favorable for tumors with extraocular extension. In these cases, chemotherapy and/or radiotherapy have been adopted. Recent reports have showed tumor response after the administration of a regimen including vincristine, carboplatin and etoposide underlining the possible use of preoperative chemotherapy to limit the aggressiveness of surgery (Meel et al. 2010). The successful use of brachytherapy after conservative surgery has also been reported (Cassoux et al. 2010).

MEP may also arise from the optic nerve from where it may extend anteriorly into the ocular globe or posteriorly, intracranially. Enucleation with resection of the optic nerve is the usual therapeutic approach. When radiotherapy and chemotherapy have been implemented, there is conflicting results (Chavez et al. 2004).

A small series of MEP arising in the central nervous system has been published, and the most common location is the periventricular region; however, the prognosis is poor (Molloy et al. 1996).

42.4 Chordoma

Gianni Bisogno

Chordoma is a rare but aggressive tumor that occurs in the spine. It is believed to arise from notochord remnants located along the craniovertebral axis. The notochord develops during the third week of gestation and is located in the central portion of the future vertebral bodies. When vertebrae develop, the notochord cells form the nucleus pulposis of the intervertebral discs. It has never been shown that intravertebral discs are the site of origin of chordoma, but the fact that this tumor most frequently arises in the sacrococcygeal and sphenooccipital regions, where ectopic notochord remnants are most often found in fetuses, and with the morphological similarities between notochord and chordoma cells supports this view.

It has been estimated that about 300 new cases of chordoma/year occur in the United States, and this correspond to an incidence of approximately one case per million people/year (McMaster et al. 2001).The median age at presentation is 60 years. It is extremely rare in children and young adults where it represents less than 5% of all chordomas. No sex predisposition has been described.

Chordoma etiology is unknown. Rarely, families with multiple affected members have been reported, suggesting an inherited condition. Although extremely rare, chordoma in children and young adults present distinctive clinical and pathological characteristics but share with adults the same unsatisfactory prognosis.

42.4.1 Clinical Characteristics

In younger patients, chordoma more frequently arises at the base of the skull, including the clivus, rather than in the mobile spine and sacrum which are the typical site in adults (Hoch et al. 2006). Very rarely, chordoma can occur outside the spine.

The tumor tends to remain localized, but the risk of distant dissemination seems higher in children under 5 years, with metastasis most frequently in the lungs, but also in lymph nodes, bone, liver kidney, adrenal gland, and heart (Borba et al. 1996).

Chordoma is generally a slow-growing neoplasm and causes symptoms from invading the nearby structures. Pain and neurological signs are more often reported: skull base tumors cause headache, cranial

nerves palsy, and torticollis, while chordoma of the spine cause alteration of bowel and/or bladder function, pain, tingling, and numbness or weakness of the arms and legs.

42.4.2 Diagnosis

Chordoma usually presents as a soft tissue mass associated with bone destruction and may extend into the intracranial compartment and sphenoid bone and sphenoid sinus. Both MRI and CT scan are employed to have a clear picture of tumor extension and bone involvement. CT shows an enhancing soft tissue mass with internal densities thought to represent fragments of bone and invasion of surrounding structures. On MRI, the lesion presents variable intensity and enhancement on T1-weighted images and high signal intensity on T2-weighted images (Lui et al. 2011).

A total body CT scan is also indicated to exclude distant metastasis. Conventional (or classic) chordoma is histologically characterized by a lobular pattern of growth with epithelioid cells arranged in nests, sheets, and syncytial cords in an abundant mucoid matrix.

The cells show some degree of nuclear atypia, the number of mitosis is usually low, and some necrosis may be present. Immunohistochemistry is usually positive for cytokeratin, epithelial membrane antigen, vimentin, S-100 protein, and variably for carcinoembryonic antigen and NSE. According to Louis et al. (2007), two more subtypes are recognized: the chondroid chordoma that contains elements that resembles neoplastic hyaline cartilage and behaves less aggressively than the conventional type, and the dedifferentiated chordoma, rarely encountered in children. Two more subtypes have been described in the pediatric age: (a) the cellular chordoma, possibly a conventional chordoma that lacks stroma, and (b) the poorly differentiated chordoma composed of sheets of epithelioid cells tightly packed with high nuclear/cytoplasmic ratio and distinct nucleoli. This latter variant affects very young children, behaving aggressively, tending to grow rapidly, and is often associated with metastasis (Hoch et al. 2006).

The differential diagnosis with chondrosarcomas may be difficult as they can occur in the same locations and share some morphological similarities (Rosenberg et al. 1999).

42.4.3 Treatment

Due to the small number of cases described in the literature, the management of pediatric cases of chordoma mainly derives from the experience gathered with adults.

Surgery has an established role, and complete tumor resection at diagnosis provides the best chances for local control and long-term survival (Park et al. 2006; Tzortzidis Elahi et al. 2006). Unfortunately, aggressive surgery is often required with a high risk of postoperative death (Borba et al. 1996) and significant morbidity (Sekhar et al. 2001). In most cases, only partial tumor resection is feasible and high-dose radiotherapy is administered. Doses in excess of 60 Gy are required, and this represents a major limitation in children. Techniques to maximize the dose of radiation to the tumor, while sparing adjacent critical structures, have been used, including proton therapy and intensity-modulated radiation therapy (IMRT). A limited number of patients have been treated so far, and the results seem promising: an overall survival of 81% has been reported in a series of 73 children and adolescents treated with proton bean radiotherapy after surgery. This compares favorably with a 55% 5-year survival described in adults with chordoma treated at the same institution (Hoch et al. 2006).

Chordomas are generally resistant to chemotherapy with only few reports describing a response to chemotherapy, including ifosfamide and doxorubicin (Scimeca et al. 1996), ifosfamide and etoposide (Dhall et al. 2011), or cisplatinum, vinblastine, and bleomycin (Azzarelli et al. 1988). The administration of 9-nitro-camptothecin in a phase 2 study including 15 patients with chordoma reported only one patient with an objective response (Chugh et al. 2005).

Recently, imatinib has been shown to have antitumor effects in some patients with advanced chordomas (Casali et al. 2004). The use of other targeted therapies such as cetixumab and gefinitinib has been reported (Hof et al. 2006).

42.4.4 Prognosis and Survival

Currently, the overall survival rate for chordoma in adults in the United States is 68% at 5 years and 40% at 10 years, with a median survival of about 7 years (McMaster et al. 2001).

Reports describing pediatric cases have shown conflicting results with some series describing worse results than in adults (Coffin et al. 1993). Recent reports of patients treated at single institutions have shown better outcome with four out of six patients alive at a median follow-up of 9 years described by Dhall et al. (2011) and an overall survival rate of 81% (median follow-up 7.2 years) in a cohort of patients with skull base chordoma referred to the Boston Massachusetts General Hospital for proton beam radiotherapy (Hoch et al. 2006). Complete tumor resection (Hug 2001) and histological subtype (Hoch et al. 2006) seem to be the major prognostic determinants. Patients with conventional chordoma have the best prognosis, while the chance of survival in the poorly differentiated subtype remains very low.

References

Intra-adrenal (Pheochromocytoma) and Extra-adrenal Paraganglioma

Auerbach SD, Steakley LS, Young Rc et al (1988) Malignant phaeochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine and dacarbazine. Ann Intern Med 109:267–273

Barontini M, Levin G, Sanso G (2006) Characteristics of pheochromocytoma in a 4- to 20-year-old population. Ann N Y Acad Sci 1073:30–37

Beltsevich DG, Kuznetsov NS, Kazaryan AM et al (2004) Pheochromocytoma surgery: epidemiologic peculiarities in children. World J Surg 28:592–596

Benn DE, Gimenez-Roqueplo AP, Reilly JR et al (2006) Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab 91: 827–836

Borba LA, Al-Mefty O (1996) Intravagal paragangliomas: report of four cases. Neurosurgery 38:569–575

Bravo EL, Kalmadi SR, Gill I (2009) Clinical utility of temozolomide in the treatment of malignant paraganglioma: a preliminary report. Horm Metab Res 41(9):703–706

Brunt LM, Lairmore TC, Doherty GM et al (2002) Adrenalectomy for familial pheochromocytoma in the laparoscopic era. Ann Surg 235:713–720

Caty MG, Coran AG, Geagen M et al (1990) Current diagnosis and treatment of pheochromocytoma in children. Experience with 22 consecutive tumors in 14 patients. Arch Surg 125:978–981

Chrisoulidou A, Kaltsas G, Ilias I et al (2007) The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer 14:569–585

Criftci AO, Tanyel FC, Senocak ME et al (2001) Phaeochromocytoma in children. J Pediatr Surg 36: 447–452

Dardik A, Eisele DW, Williams GM et al (2002) A contemporary assessment of carotid body tumor surgery. Vasc Endovascular Surg 36:277–283

Deal JE, Sever PS, Barratt TM et al (1990) Pheochromocytoma – investigation and management of 10 cases. Arch Dis Child 65:269–274

de Krijger RR, Petri BJ, van Nederveen FH et al (2006) Frequent genetic changes in childhood pheochromocytomas. Ann N Y Acad Sci 1073:166–176

Dickinson PH, Griffin SM, Guy AJ et al (1986) Carotid body tumor: 30 years experience. Br J Surg 73:14–16

Ein SH, Standling B, Wesson D et al (1990) Recurrent phaeochromocytomas in children. J Pediatr Surg 25:1063–1065

Ein SH, Pullerits J, Creighton R et al (1997) Pediatric phaeochromocytoma. A 36-year review. Pediatr Surg Int 12:595–598

Eisenhofer G, Walther MM, Huynh TT et al (2001) Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. J Clin Endocrinol Metab 86:1999–2008

Fletcher CDM, Unni KK, and Mertens F (2002) WHO Classification of Tumours. Pathology and Genetics. Tumours of Soft Tissue and Bone. IARC Press, Lyon

Goldstein RE, O'Neill JA Jr, Holcomb GW III et al (1999) Clinical experience over 48 years with pheochromocytoma. Ann Surg 229:755–764

Gonias S, Goldsby R, Matthay KK et al (2009) Phase II study of high-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. J Clin Oncol 27(25):4162–4168

Gounot E, Couillault G, Maingueneau C et al (1990) Paraganglioma of the carotid body. Apropos of a case in a 14-year-old child. Chir Pediatr 31:125–126

Gujrathi CS, Donald PJ (2005) Current trends in the diagnosis and management of the head and neck paragangliomas. Curr Opin Otolaryngol Head Neck Surg 13:339–342

Hack HA (2000) The perioperative management of children with phaeochromocytoma. Paediatr Anaesth 10:463–476

Hajnzic TF, Kruslin B, Belicza M (1999) Carotid body paraganglioma in a 9-year-old boy with extensive pulmonary metastases. Med Pediatr Oncol 32:399–400

Havekes B, Corssmit EP, Jansen JC et al (2007) Malignant paragangliomas associated with mutations in the succinate dehydrogenase D gene. J Clin Endocrinol Metab 92:1245–1248

Haws R, Joseph M, Adelman R (2007) Two cases of pheochromocytoma presenting with ADHD (attention deficit hyperactivity disorder)-like symptoms. Pediatr Nephrol 23: 473–475

Ilias I, Pacak K (2004) Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 89:479–491

Lenders JW, Pacak K, Walther MM et al (2002) Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 287:1427–1434

Lenders JW, Eisenhofer G, Mannelli M et al (2005) Phaeochromocytoma. Lancet 366:665–675

Loh KC, Fitzgerald PA, Matthay KK et al (1997) The treatment of malignant phaeochromocytoma with iodine-131 metaiodobenzylguanidine (131I-MIBG): a comprehensive review of 116 reported patients. J Endocrinol Invest 29:648–658

Ludwig AD, Feig DI, Brandt ML et al (2007) Recent advances in the diagnosis and treatment of pheochromocytoma in children. Am J Surg 194:792–796

Ong KR, Woodward ER, Killick P et al (2007) Genotype-phenotype correlations in von Hippel-Lindau disease. Hum Mutat 28:143–149

Ophir D (1991) Familiar multicentric paragangliomas in a child. J Laryngol Otol 105:376–380

Pacak K, Linehan WM, Eisenhofer G et al (2001) Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med 134:315–329

Pacak K, Eisenhofer G, Ahlman H et al (2007) Pheochromocytoma: recommendations for clinical practice from the first international symposium, October 2005. Nat Clin Pract Endocrinol Metab 3:92–102

Pellitteri PK, Rinaldo A, Myssiorek D et al (2004) Paragangliomas of the head and neck. Oral Oncol 40:563–575

Pham TH, Moir C, Thompson GB et al (2006) Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. Pediatrics 118:1109–1117

Sawka AM, Jaeschke R, Singh RJ et al (2003) A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 88:553–558

Shamblin WR, ReMine WH, Sheps SG et al (1971) Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. Am J Surg 122:732–739

Sisson JC, Shapiro B, Shulkin BL et al (1999) The treatment of malignant phaeochromocytoma with 131-I metaiodobenzylguanidine and chemotherapy. Am J Clin Oncol 22:364

Spoudeas HA, Harrison B (2005) Paediatric endocrine tumours. The British Society of Paediatric Endocrinology and Diabetes and the UK Children's Cancer Study Group, West Sussex

Stringel G, Ein SH, Creighton R et al (1980) Pheochromocytoma in children – an update. J Pediatr Surg 15:496–500

Takautz TM, Pratt CB, Jenkins JJ et al (2003) Pediatric extraadrenal paragaglioma. J Pediatr Surg 38:1317–1321

Thompson JW, Cohen SR (1989) Management of bilateral carotid body tumors and a glomus jugulare tumor in a child. Int J Pediatr Otorhinolaryngol 17:75–87

Timmers HJ, Kozupa A, Chen CC et al (2007a) Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. J Clin Oncol 25:2262–2269

Timmers HJ, Kozupa A, Eisenhofer G et al (2007b) Clinical presentations, biochemical phenotypes, and genotype-phenotype correlations in patients with succinate dehydrogenase subunit B-associated pheochromocytomas and paragangliomas. J Clin Endocrinol Metab 92:779–786

van der Mey AG, Jansen JC, van Baalen JM (2001) Management of carotid body tumors. Otolaryngol Clin North Am 34:907–924

Velchik M, Alavi A, Kresse LH (1989) Localisation of phaeochromocytoma. MIBG, CT and MR correlation. J Nucl Med 30:328–336

Weise M, Merke DP, Pacak K et al (2002) Utility of plasma free metanephrines for detecting childhood pheochromocytoma. J Clin Endocrinol Metab 87:1955–1960

Zaupa P, Höllwarth ME (2007) Carotid body paraganglioma: rare tumor in a 15-year-old adolescent boy. J Pediatr Surg 42:E13–E17

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Almeida MQ, Fragoso MCBV, Lotfi CFP et al (2008) Expression of insulin-like growth factor-II and its receptor in pediatric and adult adrenocortical tumors. J Clin Endocrinol Metab 93:3524–3531

Ariffin H, Martel-Planche G, Daud SS, Ibrahim K, Hainaut P (2008) Li-Fraumeni syndrome in a Malaysian kindred. Cancer Genet Cytogenet 186:49–53

Ayass M, Gross S, Harper J (1991) High-dose carboplatinum and VP-16 in treatment of metastatic adrenal carcinoma. Am J Pediatr Hematol Oncol 13:470–472

Barlaskar FM, Hammer GD (2007) The molecular genetics of adrenocortical carcinoma. Rev Endocr Metab Disord 8:343–348

Barlaskar FM, Spalding AC, Heaton JH et al (2009) Preclinical targeting of the type I insulin-like growth factor receptor in adrenocortical carcinoma. J Clin Endocrinol Metab 94: 204–212

Bernstein L, Gurney JG (1999) Carcinomas and other malignant epithelial neoplasms. In: Ries LAG, Smith MA, Gurney JG et al (eds) Cancer and survival among children and adolescents: United States SEER program 1975–1995. National Cancer Institute, SEER program, Bethesda, pp 139–147

Birch J, Alston RD, McNally RJQ et al (2001) Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene 20:4621–4628

Boulle N, Logie A, Gicquel C, Perin L, Le Bouc Y (1998) Increased levels of insulin-like growth factor II (IGF-II) and IGF binding protein-2 are associated with malignancy in sporadic adrenocortical tumors. J Clin Endocrinol Metab 83:1713–1720

Bugg MF, Ribeiro RC, Roberson PK et al (1994) Correlation of pathologic features with clinical outcome in pediatric adrenocortical neoplasia. Am J Clin Pathol 101:625–629

Ciftci AO, Senocak ME, Tanyel FC, Buyukpamukcu N (2001) Adrenocortical tumors in children. J Pediatr Surg 36:549–554

Coelho Netto AS, Wajchenberg BL, Ravaglia C et al (1963) Treatment of adrenocortical cancer with o,p′-DDD. Ann Intern Med 59:74–78

Crucitti F, Bellantone R, Ferrante A, Boscherini M, Crucitti P (1996) The Italian registry for adrenal cortical carcinoma: analysis of a multiinstitutional series of 129 patients. The ACC Italian Registry Study Group. Surgery 119:161–170

De Leon DD, Lange BJ, Walterhouse D, Moshang T (2002) Long-term (15 years) outcome in an infant with metastatic adrenocortical carcinoma. J Clin Endocrinol Metab 87:4452–4456

de Reynies A, Assie G, Rickman DS et al (2009) Gene expression profiling reveals a new classification of adrenocortical tumors and identifies molecular predictors of malignancy and survival. J Clin Oncol 27:1108–1115

DiGiammarino EL, Lee AS, Cadwell C et al (2001) A novel mechanism of tumorigenesis involving pH-dependent destabilization of a mutant p53 tetramer. Nat Struct Biol 9:12–16

Doghman M, Karpova T, Rodrigues GA et al (2007) Increased steroidogenic factor-1 dosage triggers adrenocortical cell proliferation and cancer. Mol Endocrinol 21:2968–2987

Dohna M, Reincke M, Mincheva A, Allolio B, Solinas-Toldo S, Lichter P (2000) Adrenocortical carcinoma is characterized by a high frequency of chromosomal gains and high-level amplifications. Genes Chromosomes Cancer 28:145–152

Driver CP, Birch J, Gough DCS, Bruce J (1998) Adrenal cortical tumors in childhood. Pediatr Hematol Oncol 15:527–532

Erickson LA, Jin L, Sebo TJ et al (2001) Pathologic features and expression of insulin-like growth factor-2 in adrenocortical neoplasms. Endocr Pathol 12:429–435

Figueiredo BC, Stratakis CA, Sandrini R et al (1999) Comparative genomic hybridization analysis of adrenocortical tumors of childhood. J Clin Endocrinol Metab 84:1116–1121

Figueiredo BC, Sandrini R, Zambetti GP et al (2006) Penetrance of adrenocortical tumours associated with the germline TP53 R337H mutation. J Med Genet 43:91–96

Gicquel C, Bertagna X, Gaston V et al (2001) Molecular markers and long-term recurrences in a large cohort of patients with sporadic adrenocortical tumors. Cancer Res 61: 6762–6767

Gonzalez RJ, Shapiro S, Sarlis N et al (2005) Laparoscopic resection of adrenal cortical carcinoma: a cautionary note. Surgery 138:1078–1086

Gonzalez KD, Noltner KA, Buzin CH et al (2009) Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol 27:1250–1256

Hanna AM, Pham TH, Skegard-Giesmann JR et al (2008) Outcome of adrenocortical tumors in children. J Pediatr Surg 43:843–849

Harrison LE, Gaudin PB, Brennan MF (1999) Pathologic features of prognostic significance for adrenocortical carcinoma after curative resection. Arch Surg 134:181–185

Hoffer FA, Daw NC, Xiong X et al (2009) A phase 1/pilot study of radiofrequency ablation for the treatment of recurrent pediatric solid tumors. Cancer 115:1328–1337

Hovi L, Wikström S, Vettenrante K, Heikkilä P, Saarinen-Pihkala UM (2003) Adrenocortical carcinoma in children: a role for etoposide and cisplatin adjuvant therapy? Preliminary report. Med Pediatr Oncol 40:324–326

Hoyme HE, Seaveer LH, Jones KL, Procopio F, Crooks W, Feingold M (1998) Isolated hemihyperplasia (Hemihypertrophy): report of a prospective multicenter study of the incidence of neoplasia and review. Am J Med Genet 79:274–278

Ilvesmaki V, Kahri AI, Miettinen PJ, Voutilainen R (1993) Insulin-like growth factors (IGFs) and their receptors in adrenal tumors: high IGF-II expression in functional adrenocortical carcinomas. J Clin Endocrinol Metab 77: 852–858

Kardar AH (2001) Rupture of adrenal carcinoma after biopsy. J Urol 166:984

Kendrick ML, Lloyd R, Erickson L et al (2001) Adrenocortical carcinoma: surgical progress or status quo? Arch Surg 136:543–549

Khayat CM, Johnston DL (2004) Rhabdomyosarcoma, osteosarcoma, and adrenocortical carcinoma in a child with a germline p53 mutation. Pediatr Blood Cancer 43:683–686

Kirschner LS (2002) Signaling pathways in adrenocortical cancer. Ann N Y Acad Sci 968:222–239

Kirschner LS (2006) Emerging treatment strategies for adrenocortical carcinoma: a new hope. J Clin Endocrinol Metab 91:14–21

Kleihues P, Schäuble B, zur Hausen A, Estève J, Ohgaki H (1997) Tumors associated with p53 germline mutations. A synopsis of 91 families. Am J Pathol 150:1–13

Langer P, Cupisti K, Bartsch DK et al (2002) Adrenal involvement in multiple endocrine neoplasia type 1. World J Surg 26:891–896

Lee JE, Berger DH, el-Naggar AK et al (1995) Surgical management, DNA content, and patient survival in adrenal cortical carcinoma. Surgery 118:1090–1098

Leung LYJ, Leung WY, Chan KF, Fan TW, Chung KW, Chan CHS (2002) Ruptured adrenocortical carcinoma as a cause of paediatric acute abdomen. Pediatr Surg Int 18: 730–732

Loncarevic IF, Herin A, Pososrki N, Linden T, Hoyer H, Bucksy P (2008) Number of genomic imbalances correlates with the overall survival for adrenocortical cancer in childhood. Pediatr Blood Cancer 51:356–362

Mackie GC, Shulkin BL, Ribeiro RC et al (2006) Use of [18F] fluorodeoxyglucose positron emission tomography in evaluating locally recurrent and metastatic adrenocortical carcinoma. J Clin Endocrinol Metab 91:2665–2671

Michalkiewicz EL, Sandrini R, Bugg MF et al (1997) Clinical characteristics of small functioning adrenocortical tumors in children. Med Pediatr Oncol 28:175–178

Michalkiewicz E, Sandrini R, Figueiredo B et al (2004) Clinical and outcome characteristics of children with adrenocortical tumors. An analysis of 254 cases from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol 22:838–845

Murphy JJ, Tawfeeq M, Chang B, Nadel H (2008) Early experience with PET/CT scan in the evaluation of pediatric abdominal neoplasms. J Pediatr Surg 43:2186–2192

Narasimhan KL, Samujh R, Bhansali A et al (2003) Adrenocortical tumors in childhood. Pediatr Surg Int 19:432–435

Ostuni JA, Roginsky MS (1975) Metastatic adrenal cortical carcinoma: documented cure with combined chemotherapy. Arch Intern Med 135:1257–1258

Pianovski MAD, Maluf EMCP, de Carvalho DS et al (2006) Mortality rate of adrenocortical tumors in children Under 15 years of age in Curitiba, Brazil. Pediatr Blood Cancer 47:56–60

Reincke M, Karl M, Travis WH et al (1994) p53 mutations in human adrenocortical neoplasms: immunohistochemical and molecular studies. J Clin Endocrinol Metab 78: 790–794

Ribeiro RC, Figueiredo B (2004) Childhood adrenocortical tumours. Eur J Cancer 40:1117–1126

Ribeiro RC, Sandrini Neto R, Schell MJ, Lacerda L, Sambaio GA, Cat I (1990) Adrenocortical carcinoma in children: a study of 40 cases. J Clin Oncol 8:67–74

Ribeiro J, Ribeiro RC, Fletcher BD (2000) Imaging findings in pediatric adrenocortical carcinoma. Pediatr Radiol 30: 45–51

Ribeiro RC, Sandrini F, Figueiredo B et al (2001) An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proc Natl Acad Sci USA 98:9330–9335

Rodriguez-Galindo C, Figueiredo BC, Zambetti GP, Ribeiro RC (2005) Biology, clinical characteristics, and management of

adrenocortical tumors in children. Pediatr Blood Cancer 45:265–273
Rosati R, Cerrato F, Doghman M et al (2008) High frequency of loss of heterozygosity at 11p15 and IGF2 overexpression are not related to clinical outcome in childhood adrenocortical tumors positive for the R337H TP53 mutation. Cancer Genet Cytogenet 186:19–24
Rossbach H-C, Baschinsky D, Wynn T, Obzut D, Sutcliffe M, Tebbi C (2008) Composite adrenal anaplastic neuroblastoma and virilizing adrenocortical tumor with germline TP53 R248W mutation. Pediatr Blood Cancer 50:681–683
Sandrini R, Ribeiro RC, DeLacerda L (1997) Childhood adrenocortical tumors. J Clin Endocrinol Metab 7:2027–2031
Slooten HV, Schaberg A, Smeenk D, Moolenaar AJ (1985) Morphologic characteristics of benign and malignant adrenocortical tumors. Cancer 55:766–773
Steenman M, Westerveld A, Mannens M (2000) Genetics of Beckwith-Wiedemann Syndrome-associated tumors: common genetic pathways. Genes Chromosomes Cancer 28:1–13
Stewart JN, Flageole H, Kavan P (2004) A surgical approach to adrenocortical tumors in children: the mainstay of treatment. J Pediatr Surg 39:759–763
Stojadinovic A, Ghossein RA, Hoos A et al (2002) Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. J Clin Oncol 20:941–950
Sutter JA, Grimberg A (2006) Adrenocortical tumors and hyperplasias in childhood – etiology, genetics, clinical presentation and therapy. Pediatr Endocrinol Rev 4:32–39
Teinturier C, Pauchard MS, Brugieres L, Landais P, Chaussain JL, Bougneres PF (1999) Clinical and prognostic aspects of adrenocortical neoplasms in childhood. Med Pediatr Oncol 32:106–111
Tissier F, Cavard C, Groussin L et al (2005) Mutations of {beta}-catenin in adrenocortical tumors: activation of the Wnt signaling pathway Is a frequent event in both benign and malignant adrenocortical tumors. Cancer Res 65:7622–7627
Tucci JR, Martins ACP, Suaid HJ et al (2005) The impact of tumor stage on prognosis in children with adrenocortical carcinoma. J Urol 174:2338–2342
Varan A, Unal S, Ruacan S, Vidinlisan S (2000) Adrenocortical carcinoma associated with adrenogenital syndrome in a child. Med Pediatr Oncol 35:88–90
Varley JM, McGown G, Thorncroft M et al (1999) Are there low-penetrance TP53 alleles? Evidence from childhood adrenocortical tumors. Am J Hum Genet 65:995–1006
Wagner J, Portwine C, Rabin K, Leclerc J-M, Narod SA, Malkin D (1994) High frequency of germline p53 mutations in childhood adrenocortical cancer. J Natl Cancer Inst 86:1707–1710
Wajchenberg BL, Pereira MAA, Medonca BB et al (2000) Adrenocortical carcinoma: clinical and laboratory observations. Cancer 88:711–736
Wang X, Liang L, Jiang Y (2007) Nine cases of childhood adrenal tumour presenting with hypertension and a review of the literature. Acta Paediatr 96:930–934
Weber MM, Fottner C, Schmidt P et al (1999) Postnatal overexpression of insulin-like growth factor II in transgenic mice is associated with adrenocortical hyperplasia and enhanced steroidogenesis. Endocrinology 140:1537–1543
Weber MM, Fottner C, Wolf E (2000) The role of the insulin-like growth factor system in adrenocortical tumorigenesis. Eur J Clin Invest 30(suppl 3):69–75
Weiss LM (1984) Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol 8:163–169
Weiss LM, Medeiros LJ, Vickery AL (1989) Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol 13:202–206
West AN, Ribeiro RC, Jenkins J et al (2006) Identification of a novel germ line variant hotspot mutant p53-R175L in pediatric adrenal cortical carcinoma. Cancer Res 66:5056–5062
West AN, Neale GA, Pounds S et al (2007) Gene expression profiling of childhood adrenocortical tumors. Cancer Res 67:600–608
Wieneke JA, Thompson LDR, Heffess CS (2003) Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. Am J Surg Pathol 27:867–881
Wood BJ, Abraham J, Hvizda JL, Alexander HR, Fojo T (2003) Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. Cancer 97:554–560
Wooten MD, King DK (1993) Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. Cancer 72:3145–3155
Zancanella P, Pianovski MAD, Oliveira BH et al (2006) Mitotane associated with cisplatin, etoposide, and doxorubicin in advanced childhood adrenocortical carcinoma. Mitotane monitoring and tumor regression. J Pediatr Hematol Oncol 28:513–524

Medulloepithelioma

Broughton WL, Zimmerman LE (1978) A clinicopathologic study of 56 cases of intraocular medulloepitheliomas. Am J Ophthalmol 85(3):407–418
Carrillo R, Streeten BW (1979) Malignant teratoid medulloepithelioma in an adult. Arch Ophthalmol 97(4):695–699
Cassoux N, Charlotte F, Sastre X et al (2010) Conservative surgical treatment of medulloepithelioma of the ciliary body. Arch Ophthalmol 128(3):380–381
Chavez M, Mafee MF, Castillo B et al (2004) Medulloepithelioma of the optic nerve. J Pediatr Ophthalmol Strabismus 41(1):48–52
Chung EM, Specht CS, Schroeder JW (2007) From the archives of the AFIP: pediatric orbit tumors and tumor like lesions: neuroepithelial lesions of the ocular globe and optic nerve. Radiographics 27(4):1159–1186
Meel R, Chawla B, Mohanti BK et al (2010) Ocular medulloepithelioma chemosensitivity. Ophthalmology 117(12):2440.e1–2440.e2
Molloy PT, Yachnis AT, Rorke LB et al (1996) Central nervous system medulloepithelioma: a series of eight cases including two arising in the pons. J Neurosurg 84:430–436
Priest JR, Williams GM, Manera R et al (2011) Ciliary body medulloepithelioma: four cases associated with pleuropulmonary blastoma–a report from the International Pleuropulmonary Blastoma Registry. Br J Ophthalmol 95(7):1001–1005
Vajaranant TS, Mafee MF, Kapur R et al (2005) Medulloepithelioma of the ciliary body and optic nerve: clinicopathologic, CT, and MR imaging features. Neuroimaging Clin N Am 15(1):69–83

Viswanathan S, Mukul S, Qureshi S et al (2008) Orbital medulloepitheliomas – with extensive local invasion and metastasis a series of three cases with review of literature. Int J Pediatr Otorhinolaryngol 72:971–975

Chordoma

Azzarelli A, Quagliuolo V, Cerasoli S et al (1988) Chordoma: natural history and treatment results in 33 cases. J Surg Oncol 37(3):185–191

Borba LA, Al-Mefty O, Mrak RE et al (1996) Cranial chordomas in children and adolescents. J Neurosurg 84(4): 584–591

Casali PG, Messina A, Stacchiotti S et al (2004) Imatinib mesylate in chordoma. Cancer 101(9):2086–2097

Chugh R, Dunn R, Zalupski MM et al (2005) Phase II study of 9-nitro-camptothecin in patients with advanced chordoma or soft tissue sarcoma. J Clin Oncol 23(15): 3597–3604

Coffin CM, Swanson PE, Wick MR et al (1993) Chordoma in childhood and adolescence. A clinicopathologic analysis of 12 cases. Arch Pathol Lab Med 117(9):927–933

Dhall G, Traverso M, Finlay JL et al (2011) The role of chemotherapy in pediatric clival chordomas. J Neurooncol 103(3):657–662

Dr. Ferrari or Dr. Bisogno, Tsai EC, Santoreneos S, Rutka JT (2002) Tumors of the skull base in children: review of tumor types and management strategies. Neurosurg Focus. May 15;12(5):e1

Hoch BL, Nielsen GP, Liebsch NJ et al (2006) Base of skull chordomas in children and adolescents: a clinicopathologic study of 73 cases. Am J Surg Pathol 30(7):811–818

Hof H, Welzel T, Debus J (2006) Effectiveness of cetuximab/gefitinib in the therapy of a sacral chordoma. Onkologie 29(12):572–574

Hug EB (2001) Review of skull base chordomas: prognostic factors and long-term results of proton-beam radiotherapy. Neurosurg Focus 10(3):E11

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (2007) WHO Classification of Tumours of the Central Nervous System, 4th edn. International Agency for Research on Cancer: Lyon

Lui YW, Dasari SB, Young RJ (2011) Sphenoid masses in children: radiologic differential diagnosis with pathologic correlation. AJNR Am J Neuroradiol 32(4):617–626

McMaster ML, Goldstein AM, Bromley CM et al (2001) Chordoma: incidence and survival patterns in the United States, 1973-1995. Cancer Causes Control 12:1–11

Park L, Delaney TF, Liebsch NJ et al (2006) Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. Int J Radiat Oncol Biol Phys 65(5):1514–1521

Rosenberg AE, Nielsen GP, Keelet SB et al (1999) Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol 23(11):1370–1378

Scimeca PG, James-Herry AG, Black KS et al (1996) Chemotherapeutic treatment of malignant chordoma in children. J Pediatr Hematol Oncol 18(2):237–240

Sekhar LN, Pranatartiharan R, Chanda A et al (2001) Chordomas and chondrosarcomas of the skull base: results and complications of surgical management. Neurosurg Focus 10(3):E2

Tzortzidis Elahi F, Wright D et al (2006) Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. Neurosurgery 59:230–237

Part X

Rare Tumors of the Skin and Subcutaneous Tissue

Rare Tumors of the Skin and Subcutaneous Tissues

43

Alberto S. Pappo, Thomas K. Eigentler, Claus Garbe, Paola Collini, Andrea Ferrari, and Jochen Rössler

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43.1 Differential Diagnosis of Cutaneous Tumors

The clinical diagnosis of cutaneous tumors in a child may be a challenge not only due to the rarity of the diseases but also because benign lesions may have alarmingly malignant tumor-like features as well as malignant neoplasms may present with benign characteristics (i.e., pedunculated or amelanotic melanoma simulating a pyogenic granuloma). The same can be said for the pathological diagnosis. For some histotypes, the histological diagnosis of a tumor of the skin in a child can be very difficult for many reasons. For example, the diagnosis of melanoma in pediatric

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age has often been a problem for pathologists. Melanoma is a very rare entity in children, so pathologists are always psychologically tempted to find an alternative diagnosis. Actually, pediatric melanomas do exist and deserve a distinct treatment. In pediatric age, the histological characteristics of melanoma are mimicked by other more frequent neoplasms, i.e., Spitz tumors, for which a spectrum of aggressiveness is reported from benign lesions (Spitz nevi) through the so-called atypical lesions (atypical Spitz tumors, with a risk ranging from low to high) up to the Spitzoid melanoma. Moreover, the borders between these entities are not so sharply defined. The misdiagnosis of pigmented lesions may be common in pediatric age. As an example, a study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) reported that, among 102 lesions originally diagnosed as melanoma in children, only 60 were confirmed as being malignant at histological review, while 42 were reclassified as benign (Spatz et al. 1996). In this very complex scenario, a further issue is the attitude of dermatopathologists of adults to apply adult-type histological criteria and classify pediatric lesions into adult-type categories. In the end, on one side, there is the risk of underdiagnosing malignant tumors due to the conviction that melanoma and other malignant diseases are virtually nonexistent in the young, and patients may pay the price of this in terms of uncorrected treatment approach, advanced disease at the time of the diagnosis, and – ultimately – in terms of survival. On the other side, there is the risk of overdiagnosis and therefore overtreatment of benign lesions. All these facts underline the importance of referring suspected cases to expert physicians who are professionally dedicated to skin tumors – also in the light that early diagnosis remains the most reliable way to cure melanoma and other cutaneous tumors. For clinicians, it is not so much a matter of pediatric oncologists being capable of diagnosing melanoma but of their knowing that it does occur in children and referring any suspected cases to experts dedicated to melanoma. For pathologists, pediatric melanocytic lesions of the skin should be diagnosed by a pathologist aware of pediatric skin pathology. The creation of panel of experts, the building of network of cooperation, the centralized review, and the option of second opinion are possible suggestions to improve the quality of pathological diagnosis of childhood skin tumors.

43.2 Cutaneous Melanoma

Alberto Pappo, Thomas K. Eigentler, Claus Garbe, Paola Collini, and Andrea Ferrari

Melanoma in children and adolescents is rare, accounting for less than 3% of cancers in patients under 20 years of age and for 7% of all cancers in 15–19-year-olds (Fig. 43.1) (Ries et al. 1999). The melanoma age-adjusted specific incidence rate in patients under 20 years is 5.8 per million (http://seer.cancer.gov/csr/1975_2007/results_merged/sect_29_childhood_cancer_iccc.pdf), and current estimates suggest that there are approximately 427 new cases of melanoma diagnosed each year in the United States in patients under the age of 20 (Bleyer et al. 2006). Melanoma is more common in young females, and males predominate after the age of 40 years. In a review by Strouse, the incidence of pediatric melanoma was reported to have increased at a rate of 2.9% per year over a 28-year period after adjusting for age, race, sex, and ambient UV radiation (Strouse et al. 2005). In this study, adolescents and young adults had higher increases in incidence rates when compared to younger patients. Epidemiological studies have demonstrated that the melanoma incidence increases with age; over 90% of cases occur in patients older than 10 years of age, and 74% are seen in those aged 15–19 years (Bleyer et al. 2006). Melanoma most commonly affects fair-skinned individuals; in two epidemiological studies, more than 90% of patients over the age of 10 years were white (Strouse et al. 2005; Lange et al. 2007). Major increases were seen in males between 1975 and 1979 as well as 1975 and 1999 and also in whites, particularly in ages 5–9 and ages 15–19 years.

A study from the Italian TREP project (Tumori Rari in Età Pediatrica [*rare tumors in pediatric age*]) analyzed the incidence of rare tumors included in the TREP list on the basis of a definition of annual incidence of less than two cases per million population. Using the data from the population-based cancer registries AIRTUM (that covers 33% of the Italian resident population in the 0–14-year-old age group and 27% of the 15–19-year-old age group), the study reported that annual incidence of melanoma was less than 2 per million population among 0–10-year-olds (0.64 for 1–4- and 0.30 for 5–9-year-olds) but was higher than 2 per million population in the age ranges

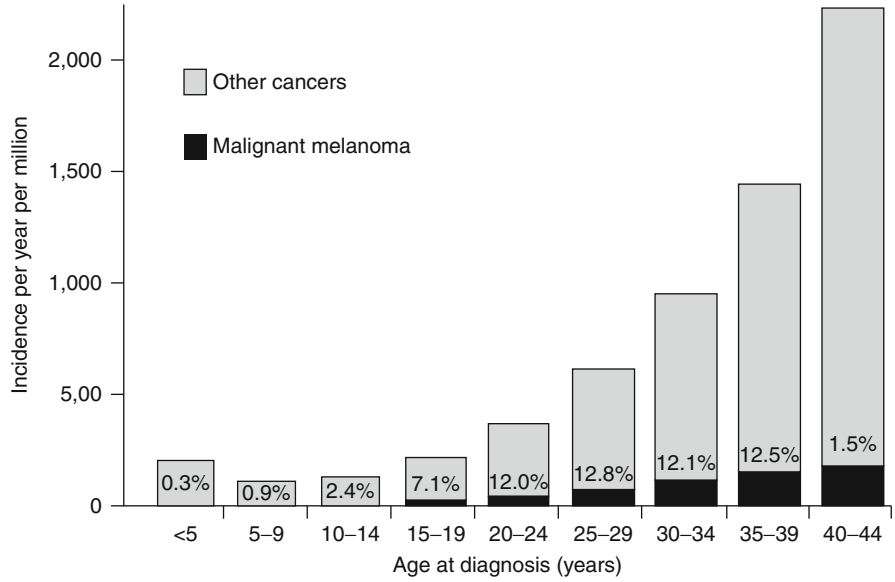

Fig. 43.1 Incidence of pediatric melanoma

over 10 years, being, in particular, 2.38 for 10–14- and 8.78 for 15–17-year-olds. In other words, melanoma would be a "rare pediatric tumors" – as defined by the TREP group – in children < 10 years, but not in older ones and, in particular, in adolescents (Pastore et al. 2009).

43.2.1 Risk Factors

Several risk factors for the development of adult melanoma have been observed in children. These include light pigmentary traits, tendency to freckle, and increased number of melanocytic nevi (Youl et al. 2002). However, a subset of pediatric patients has unique risk factors that predispose them to the development of malignant melanoma, and these include:

1. Xeroderma pigmentosum. This autosomal recessive disorder is characterized by extreme photosensitivity to ultraviolet radiation and mutations of the nucleotide excision repair complementation groups. Most of the skin cancers develop during the first decade of life and preferentially affect the head and neck area (Kraemer et al. 1994). Early recognition of sun sensitivity with molecular testing is essential in establishing the diagnosis. Sun avoidance is crucial, and use of high-dose oral isotretinoin has been shown to be effective in preventing new cancers in patients with multiple skin cancers (Kraemer et al. 1988).
2. Retinoblastoma. Survivors of hereditary retinoblastoma are at increased risk for developing melanoma, and this risk is seen in both irradiated and nonirradiated patients (Kleinerman et al. 2005).
3. Werner syndrome. Patients with Werner syndrome are at increased risk for developing various malignancies, including melanoma (Goto et al. 1996). This autosomal recessive syndrome is characterized by the onset of premature features associated with aging and is due to mutations of the *WRN* gene, a member of the human RecQ family of DNA helicases (Muftuoglu et al. 2008).
4. Congenital melanoma is the most common transplacentally acquired malignancy. Of six cases reported in the literature, only one is a long-term survivor. It is recommended that the placentas of all women with suspected melanoma be evaluated for the presence of the disease and that the neonate be screened for signs of disease for 24 months postpartum (Alexander et al. 2003).
5. Melanoma can arise from medium-sized and large congenital nevi and can more commonly involve the scalp (Fig. 43.2). Even though the overall risk for developing melanoma in a congenital nevus is only 0.7%, it raised with the size of the nevus. The melanoma risk is highest for those nevi designated as garment nevi.
6. Giant congenital melanocytic nevi (Fig. 43.3) affect less than 1 in 20,000 newborns. Patients with these lesions have about a 5% lifetime risk of

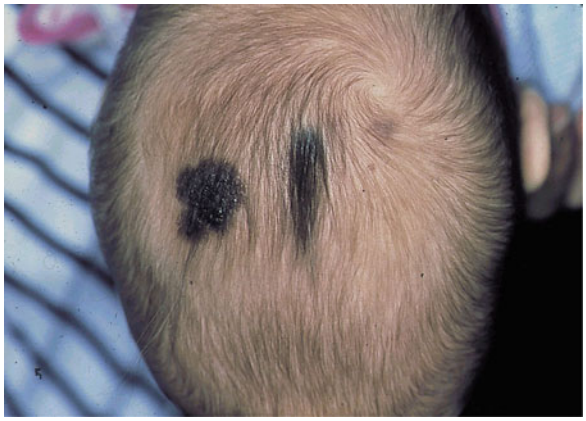

Fig. 43.2 Congenital melanoma arising in a medium-sized nevus

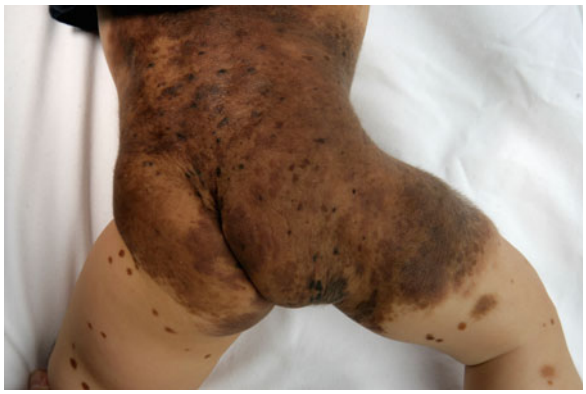

Fig. 43.3 Giant congenital melanocytic nevi

developing melanoma, and most develop early in life (Hale et al. 2005). Patients with larger-sized nevi and increased numbers of satellite nevi are at increased risk for developing melanoma.

7. Neurocutaneous melanosis is an extremely rare disorder characterized by large or multiple congenital nevi in association with meningeal melanoma or melanosis (Makkar and Frieden 2004). The likelihood of developing neurocutaneous melanosis in giant congenital nevi ranges from 2.5% to 12%, and larger nevus size and multiple satellites appear to increase the risk of this complication (Ceballos et al. 1995). Most symptomatic patients present with neurological manifestations, such as increased intracranial pressure within the first 2 years of life. Central nervous system (CNS) melanoma develops in up to 64% of patients with symptomatic disease, and the prognosis is extremely poor, with a median survival of about 6 months. Approximately 25% of asymptomatic patients with large congenital nevi have radiographic evidence by MRI of CNS melanosis. In one series, only 1 of 20 children studied developed symptomatic disease (Ceballos et al. 1995).
8. Immunosuppression. Patients with immune deficiencies and those that have undergone solid organ and bone marrow transplantation are at increased risk for developing melanoma (Curtis et al. 1997; Euvrard et al. 2003). Survivors of childhood cancer also have an increased risk of developing melanoma (Friedman et al. 2010).
9. Genetic factors. It is estimated that about 8%–10% of melanoma cases have a family history of the disease. Germline mutations in CDKN2A and CDK4 susceptibility genes have been identified in only 10–25% of familial melanoma cases, and therefore, additional undefined high-penetrance predisposition genes probably exist (e.g., the locus on chromosome band 1p22) (Hayward 2003; Whiteman et al. 1997). A recent Italian study on 21 pediatric melanoma samples was able to identify not only some genetic traits in common with melanoma of adulthood (i.e., BRAF oncogene activation and a frequent loss of the CDKN2A gene, suggesting that the tumor's pathogenesis partially coincides with that of adult melanoma) but also other traits peculiar to the younger age group (frequent c-Kit gene alterations), hinting at the involvement of novel genetic networks (Danietti et al. 2009). When known melanoma susceptibility genes were analyzed, a particular pattern emerged from the comparison with familial melanoma cases, featuring the lack of any CDKN2A germline mutations in the absence of a family history of melanoma and a marginal role for MC1R variants (suggesting a prevalent role for other genes affecting pigmentation) (Uribe et al. 2005). So, other genetic factors may play a part in sporadic childhood melanoma, probably including high-penetrance predisposition genes as well as low-penetrance polymorphic variants. A particular pattern involving the loss of heterozygosity and microsatellite instability has also been described in childhood melanoma (Uribe et al. 2005). Finally, it is worth of being quoted the genome-wide association studies (GWAS) conducted in melanoma and in other common cancer

types; these studies were able to identify novel disease loci not previously suspected to be related to carcinogenesis, confirming that tumor susceptibility is polygenic and pointing to new disease mechanisms (Easton and Eeles 2008).

10. Environmental factors. A history of sunburns in early life and tanning bed exposure also confers and increases risk for developing melanoma (Lazovich et al. 2010). An increase in the incidence of melanoma in pediatric ages has been recently observed also in Northern Europe (Karlsson et al. 1998; Pearce et al. 2003) and, particularly, in Australia (Whiteman et al. 1995; Milton et al. 1997) where the overall incidence of melanoma is 5 times more than that in Europe. In particular, melanoma in Queensland accounts for 6% of all pediatric tumors and is the seventh most frequent malignancy in children: incidence rates rise from 1 per million in the 0–4 age group to 30 per million in the 10–14 age group (Whiteman et al. 1995). This data are undoubtedly related to UV exposure, latitude, and skin type and pigmentation (fair-skinned individuals, with red hair, are more likely to develop melanoma than darkly pigmented individuals). The great awareness of physicians and parents, and the improved accuracy in histological diagnosis (e.g., diagnosis of melanoma versus atypical Spitz nevus), may play a role in the increased incidence, but the main role is played by the increased cumulative UV exposure during childhood and adolescence (e.g., increased risk of melanoma in lower extremities of girls). This data have been measured in various studies by the number of blistering sunburns and reported time spent outdoors and would confer a two to fivefold increased risk of melanoma in case-control studies of adults (Fears et al. 2002; Loria and Matos 2001; Gilchrest et al. 1999).

43.2.2 Clinical Manifestations

Melanoma in prepubertal children is a challenge even for clinicians who see pigmented skin lesions in children on a daily basis because of the alarming melanoma-like features of some benign nevi (Spitz nevi, Reed nevi, and junctional nevi) and because prepubertal melanoma often does not appear with the typical appearance of the adult forms. The disease often presents as a nodular, or a pedunculated, and/or an amelanotic lesion, sometimes simulating pyogenic granulomas (Ferrari et al. 2005; Ceballos et al. 1995; Handfield-Jones and Smith 1996; Mones and Ackerman 2003; Sybert 1991; Zuckerman et al. 2001; Sander et al. 1999; Tate et al. 1993). The commonly used ABCD clinical rule (Asymmetry – Border irregularity – Color variability – Dimension > 6 mm) may be useless and even misleading in childhood melanoma (Bono and Ferrari 2005). Regarding tumor size, for instance, is noteworthy since benign nevi normally grow up to relatively large size as the child grows, whereas, at the same time, melanomas may be frequently detected at a very small size (Bono 2001). When melanoma arises in a congenital nevus (particularly, in the case of "bathing trunk nevus," congenital darkly pigmented and often disfiguring melanocytic lesion, sometimes associated with neurofibromatosis, lipomas, and spina bifida), diagnosis is even more very difficult because malignant transformation often evolves in its deeper components and surface alterations may be a late manifestation.

Presenting features such as bleeding, ulceration, increasing mole size, itching, and a palpable mass, may be present in pediatric cases as (Kaste et al. 1996). The diagnosis of melanoma in children is often unsuspected, and in various series, misdiagnosis and diagnostic delays were reported (in up to 60% of patients) (Saenz et al. 1999; Melnik et al. 1986). In two large series of pediatric melanoma from the SEER and National Cancer databases, female sex predominated, and two thirds of patients presented with localized disease; less than 5% of patients presented with distant metastatic disease (Strouse et al. 2005; Lange et al. 2007). In these series, over 90% of children were white, and the most common histologic subtype was superficial spreading melanoma. Thin and intermediate-thickness lesions were more commonly observed, and thick lesions, defined as those >4 mm in thickness, were seen in only 2% of cases. In both series, younger patients were more likely to be nonwhite, present with disseminated disease, and have nodular histology, head and neck primaries, history of cancer in the family, thicker lesions, and an inferior clinical outcome (Strouse et al. 2005; Lange et al. 2007). Others reported better outcome for younger patients compared to adolescents and adults (Ferrari et al. 2005).

The clinical characteristics of melanoma in children were studied in an evaluation of the database of the

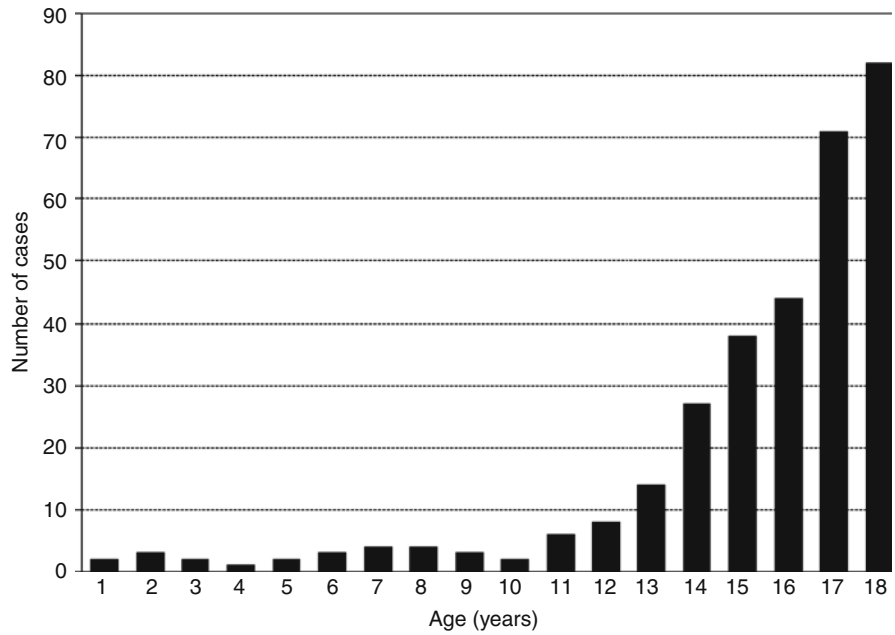

Fig. 43.4 Age distribution of patients with cutaneous melanoma in childhood and adolescence (German Central Malignant Registry, 1983–2004; 54,033 patients, 316 patients <18 years old)

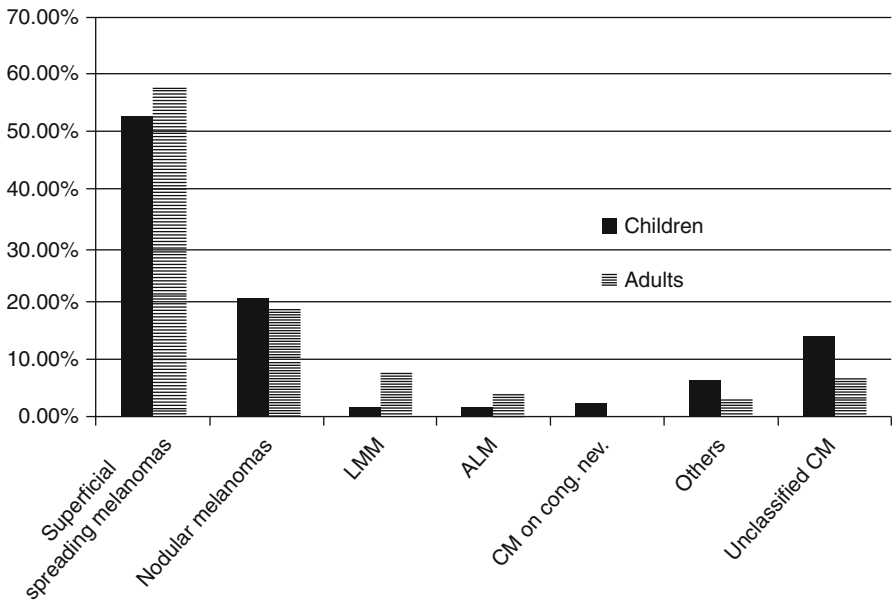

Fig. 43.5 Histopathological subtypes of cutaneous melanomas in children up to the age of 18 (German Central Malignant Registry, 1983–2004)

Central Malignant Registry in Germany. During the time from 1983 to 2004, 60 dermatologic departments contributed to this database, and 54,033 patients with cutaneous melanomas were documented. Only 316 patients (0.6%) were found with an age up to 18 years. The age distribution of these patients is given in Fig. 43.4. There were only very few cases up to the age of 12 years. In the age of 13–18 years, the prevalence of melanoma patients increased rapidly. As this kind of data collection is based on the histopathologic reports of the documenting centers, there are no clear data on how many misdiagnoses are among these melanoma reports for children.

Regarding the melanoma subtypes, mainly superficial spreading melanomas and nodular melanomas were reported. As expected, there are a very low number of cases with lentigo maligna melanoma or acral lentiginous melanoma. Likewise, there are very few reports on melanomas on large or small congenital nevi (Fig. 43.5).

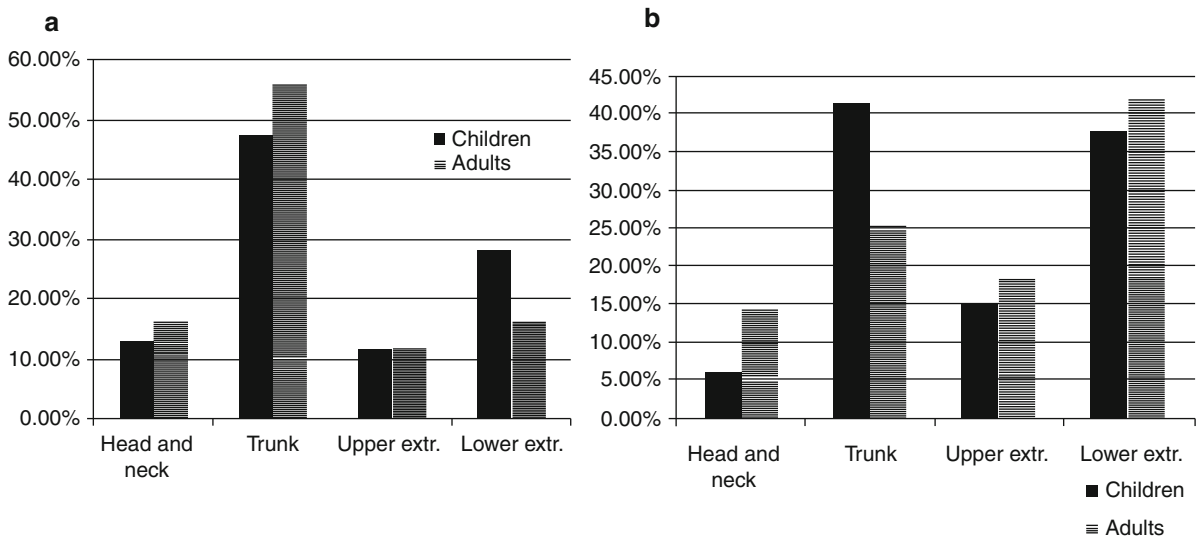

Fig. 43.6 Site distribution of melanomas in males (**a**) and females (**b**) (German Central Malignant Registry, 1983–2004)

The body sites where melanoma developed differed between male and female gender, but they were equally distributed in children as in adults. While males developed melanomas mainly on the trunk, a predilected site in females was the lower extremity. In children, however, there were, in females, more melanomas on the trunk and, in males, more melanomas on the lower extremity (Fig. 43.6).

The tumor thickness of melanomas in children was similarly distributed as in adults. Most melanomas in children were diagnosed with a tumor thickness of less than 1.0 mm. In children, even a higher percentage of patients were diagnosed with thin melanomas (Fig. 43.7). In children, tumor thickness was found to be the most important prognostic factor, and 10-year survival was best in thin melanomas, and the 10-year survival probability in children with thick melanoma with more than 4 mm in tumor thickness was around 70%. These data show that melanomas in children and adults behave very similarly and show rather equal clinical characteristics.

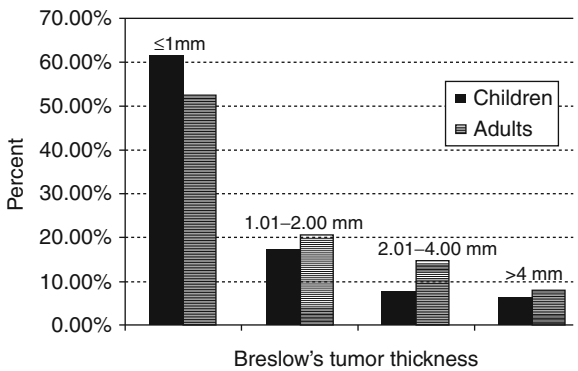

Fig. 43.7 Distribution of tumor thickness in children up to the age of 18 and in adults over 18 years of age (German Central Malignant Registry, 1983–2004)

43.2.3 Establishing the Diagnosis of Pediatric Melanoma

Back in 1948, Sophie Spitz published a landmark paper defining the term "juvenile melanoma," which described a benign nevus in childhood histologically mimicking malignant melanoma (Spitz 1948). Later on, the term "juvenile melanoma" was replaced by "Spitz nevus" to emphasize the clinical benign behavior of these lesions. Establishing the diagnosis of pediatric melanoma can be challenging, and other lesions can be confused with this diagnosis in the pediatric population. In a study of histopathologic diagnosis of malignant melanoma in childhood, a poor reliability even among experts was detected (Wechsler et al. 2002). Additionally, it seems that in retrospective reevaluations of histological specimens, knowing the clinical course of the children, the initial diagnosis of prepuberal melanoma had to be revised to benign

melanocytic lesions (Leman et al. 2005). Therefore, it is likely that several documented cases of malignant melanoma in childhood in cancer registries are benign Spitz nevus, leading to an overestimation of incidence rates in such registries.

Furthermore, the emergence of purely descriptive entities, such as Spitzoid melanoma, atypical Spitzoid lesions, melanocytic lesions or tumors of unknown metastatic potential (MELTUMP), and atypical Spitz nevus, is confusing and ill defined (Mones and Ackerman 2004), and their diagnosis places a significant responsibility on the treating clinician who is ultimately responsible for making therapeutic decisions, such as the appropriateness of complete lymph node dissections or administration of adjuvant therapies with interferon. It is important to remember that although these interventions have been well studied in adults, their long-term impact in children is unknown (Su et al. 2003; Lohmann et al. 2002; Busam et al. 2009). In one publication of 57 MELTUMP, an expert panel of dermatopathologists reviewed these lesions and matched their interpretation with the actual clinical behavior of the lesion. Only half of the participants were able to diagnose clinically favorable lesions as benign, and 73%, with unfavorable behavior as malignant. These lesions are being increasingly recognized and are biologically different from conventional melanomas or benign melanocytic nevi (Cerroni et al. 2010).

Several investigators are now relying on molecular tests to better classify the diagnosis of melanocytic tumors in children. The use of comparative genomic hybridization (Fig. 43.8a, b) and FISH has identified multiple chromosomal aberrations in melanoma that most commonly involve regions at 6p25, 6q23, 9p, 10q, 8p 1q, and 11q13 (Gerami et al. 2009; Bastian et al. 1999, 2000). These findings are not seen in patients with Spitzoid lesions, which usually have a normal chromosomal complement and occasional gains of chromosome 11p. Additionally, the detection of BRAF mutations can be helpful in differentiating between melanoma and Spitz nevi. Whereas BRAF mutations are rare in patients with Spitzoid lesions, a significant number of melanomas have a mutation in this gene (Gill et al. 2004; Brose et al. 2002). In a recent Italian paper, analysis of 21 pediatric patients with melanoma revealed CDKN2A and MC1R gene variants in 2/21 and 12/21 patients, respectively. At the somatic level, 9/14 lesions had CDKN2A locus homozygous deletions and a null p16 immunophenotype. Loss of KIT protein expression was seen in 7/14 cases, and BRAF (V600E) mutations were seen in 5/10 cases (Danietti et al. 2009).

43.2.4 Histological Diagnosis: MELTUMP

MELTUMP is a term proposed in 2004, encompassing a group of lesions that pose problems in the definition of their malignant potential as defined by the classical histological parameters. In these lesions, the application of the usual histological criteria of malignancy of conventional melanocytic lesions does not carry the same risk of malignancy. MELTUMP should not be a wastebasket for any difficult lesion. MELTUMP *are tumorigenic atypical deep compound and dermal melanocytic tumors*. They exhibit one or several features indicative of possible malignancy, such as nuclear atypia, macronucleoli, mitotic activity, necrosis, or ulceration, but they exhibit these features in number or degree insufficient to justify a diagnosis of malignancy. The term "MELTUMP" should be used for "lesions that do not display all of the characteristics that permit a diagnosis of vertical growth phase melanoma and whose capacity to metastasize is indeterminate or uncertain." This term implies a risk to progress upon incomplete excision and potential for metastasis after complete excision. MELTUMP are a heterogeneous group of lesions encompassing atypical Spitz tumors (AST), cellular and atypical epithelioid/spindled blue nevi (ABN), and minimal deviation melanomas. Also, pigmented epithelioid melanocytoma is included. In particular, presence of deep dermal mitoses in AST and of mitoses irrespective of location in ABN is considered as a marker of risk, enough to include these two entities among MELTUMP (Mones and Ackerman 2004; Busam et al. 2009; Cerroni et al. 2010).

43.2.5 Histological Diagnosis: Melanoma

To summarize, the histological diagnosis of melanoma in childhood is difficult due to many factors:

- It is a rare tumor in pediatric age, but it still exists.
- Childhood melanoma can show histological features not present in adulthood melanoma.
- Proliferative nodules in congenital nevi should be carefully distinguished from melanoma.
- Spitzoid lesions are particularly problematic, and many of them fall within MELTUMP.

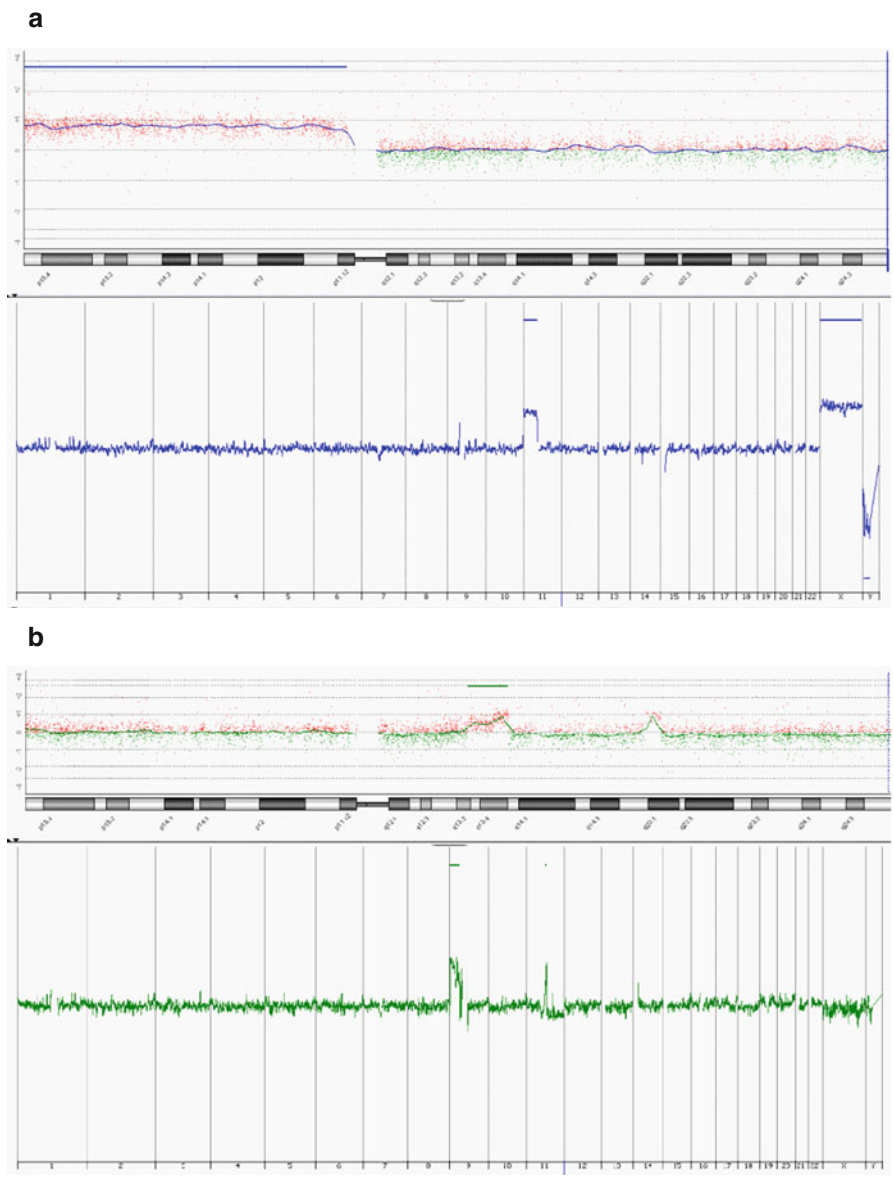

Fig. 43.8 Comparative genomic hybridization: (**a**) finding of an 11p gain typical of Spitz nevi in a 14-year-old girl; (**b**) histopathologically diagnosed as MELTUMP in a 10-year-old boy. Complex copy number aberrations on chromosomes 9 and 11. The narrow gains on chromosome 11 include cyclin D1. The genetic instability is in favor of a melanoma

The five major subtypes of melanoma in adulthood are superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral lentiginous melanoma, and mucosal lentiginous melanoma. These histotypes can be found in children. Though, in childhood, many lesions are composed by epithelioid and spindle cells with Spitzoid characteristics, and a careful differential diagnosis in the range of atypical Spitzoid tumors is required. Also, there are melanomas arising in congenital nevi that are to be carefully differentiated from proliferative nodules.

A series of features should alert the pathologist to take a diagnosis of melanoma into consideration: size larger than 7 mm, asymmetry, poorly defined borders, ulceration, marked pagetoid spread, pleomorphism, expansile dermal growth, high mitotic count (>4/mm^2), deep mitoses, atypical mitoses, absence of maturation, lymphatic/vascular invasion, and perineural diffusion. The pathologist should take into account all these

Table 43.1 TNM classification of melanoma (American Joint Committee on Cancer, AJCC. JCO 27:6199, 2009)

Stage	TNM classification	Histologic/clinical features
0	Tis N0 M0	Intraepithelial/in situ melanoma
IA	T1a N0 M0	≤1 mm without ulceration and mitotic rate <1/mm^2
IB	T1b N0 M0	≤1 mm with ulceration or mitotic rate ≥1/mm^2
	T2a N0 M0	1.01–2 mm without ulceration
IIA	T2b N0 M0	1.01–2 mm with ulceration
	T3a N0 M0	2.01–4 mm without ulceration
IIB	T3b N0 M0	2.01–4 mm with ulceration
	T4a N0 M0	4 mm without ulceration
IIC	T4b N0 M0	>4 mm with ulceration
IIIA	T1-4a N1a M0	Single regional nodal micrometastasis, nonulcerated primary
	T1-4a N2a M0	2–3 microscopic positive regional nodes, nonulcerated primary
IIIB	T1-4b N1a M0	Single regional nodal micrometastasis, ulcerated primary
	T1-4b N2a M0	2–3 microscopic regional nodes, nonulcerated primary
	T1-4a N1b M0	Single regional nodal macrometastasis, nonulcerated primary
	T1-4a N2b M0	2–3 macroscopic regional nodes, no ulceration of primary
	T1-4a/b N2c M0	In-transit met(s)* and/or satellite lesion(s) without metastatic lymph nodes
IIIC	T1-4b N2a M0	Single macroscopic regional node, ulcerated primary
	T1-4b N2b M0	2–3 macroscopic metastatic regional nodes, ulcerated primary
	Any T N3 M0	4 or more metastatic nodes, matted nodes/gross extracapsular extension, or in-transit met(s)/satellite lesion(s) and metastatic nodes
IV	Any T any N M1a	Distant skin, subcutaneous, or nodal metastases with normal LDH levels
	Any T any N M1b	Lung metastases with normal LDH
	Any T any N M1c	All other visceral metastases with normal LDH or any distant metastases with elevated LDH

features of the lesion. The presence of a single factor is not significant per se.

When a melanoma is diagnosed, the pathologist should apply the same histological parameters as in the adult case, even if their true prognostic significance could not always be superimposable in childhood. In particular, a diagnosis of primary cutaneous melanoma should include histological type, Clark level, thickness, mitoses/mm^2, type of growth phase, presence of microscopic satellites, presence of regression, presence of ulceration, tumor-infiltrating lymphocytes (TIL), neuro and vascular diffusion, associated nevus, and state of resection margins (Cerroni et al. 2010; Brenn and McKee 2008).

43.2.6 Staging

Staging guidelines have not been developed for patients with pediatric and adolescent melanoma, and therefore, most of the reported series have incorporated the adult American Joint Committee on Cancer (AJCC) classification of melanoma. In the new AJCC classification, which was modified in 2009, patients are stratified into four different groups (Table 43.1). Patients with localized disease can be classified as stage I and II based on the thickness of the primary tumor, presence or absence of ulceration, and mitotic rate. Patient with stage III disease have nodal involvement, and those with stage IV disease have distant metastatic disease. As in adults, the stage of the disease is predictive of outcome in pediatric melanoma, and thicker lesions have a higher incidence of nodal involvement (Strouse et al. 2005; Rao et al. 1990; Paradela et al. 2010) (Fig. 43.9). However, although the incidence of nodal involvement appears to be higher, particularly amongst patients with MELTUMP (Busam et al. 2009), the outcome of these patients does not appear to be significantly affected. The use of routine imaging to detect metastatic disease in children with melanoma has not been studied extensively, but one publication suggests that patients who present with thick primary lesions or lesions with an unknown primary have an increased incidence of clinically unsuspected metastases and should therefore be imaged routinely (Kaste et al. 1996).

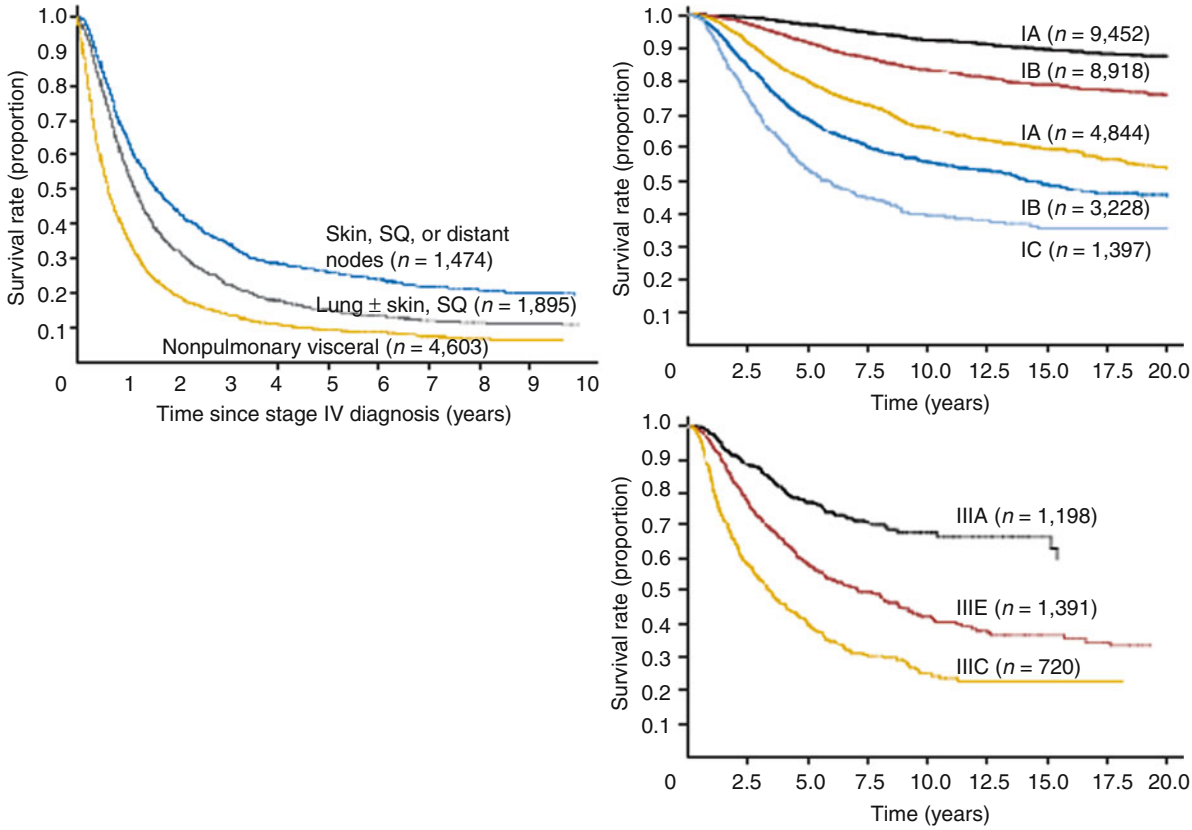

Fig. 43.9 Survival for patients with melanoma stages I–IV (reproduced with permission. JCO 27:6199, 2009)

43.2.7 Treatment

There is a general consensus that the therapeutic recommendations for childhood melanoma should remain the same as for adults. Surgical resection remains the mainstay of therapy for pediatric melanoma. When possible, we advocate following the same surgical guidelines that have been developed for adults: lesions ≤1 mm should be resected with a 1-cm margin; 1–4 mm lesions, with a 2-cm margin; and those more than 4 cm, with at least a 2-cm margin. Patients with lesions ≤1 mm and no ulceration or mitotic rate <1 mm^2 can be treated with surgical resection alone and observation. Lesions with more adverse features, such as thickness ≥0.75–1 mm, increased mitotic rate, and evidence of ulceration, including lymphovascular invasion, should undergo sentinel node sampling (Shah et al. 2006; Butter et al. 2005; Roaten et al. 2005). If the sentinel node is positive, patients should be offered a complete lymph node dissection with the caveat that only 15–20% of patients will have subsequent positive nodes and that this procedure may not impact survival (Morton et al. 2006) (Table 43.2).

The issue of medical treatment in children with melanoma is problematic. Because of the rarity of the disease and the lack of experience of pediatric oncologists in treating these tumors, pediatric patients should be included – when possible – in adult therapeutic trials (i.e., immunotherapy, immunochemotherapy, vaccinotherapy). Unfortunately, most of clinical trials are not open to children. Alpha interferon (Kirkwood et al. 2004) has shown to improve relapse-free survival in patients with high-risk resected melanoma. It has been approved in North America by the Food and Drug Administration for high-risk melanoma, and it is virtually the only adjuvant treatment currently available for children. The use of this therapy is well tolerated in children, but its efficacy has not been tested, given the small numbers of patients that have been treated in limited institutions over the years (Shah et al. 2006; Navid et al. 2005; Chao et al. 2005). For patients with metastatic disease, limited reports suggest that

Table 43.2 Practical diagnostic and treatment guidelines for pediatric melanoma

Biopsy	When should a diagnostic excision be done in front of suspected pigmented lesions? When (1) there is the well-founded clinical suspicion of malignancy, (2) the lesion evolves quickly, and (3) the lesion has atypical morphology Dermoscopy may reinforce the decision for biopsy In cases where a moderate perplexity remains, a short-term observation may be suggested (the removal of a pigmented lesion in a child will result in a significant cosmetic – and sometimes, in a functional – impairment) When excision is justified, the surgical width should be limited (to 2 mm from lesion borders) for functional and aesthetic reasons
Diagnostic work	Comprehensive guidelines for the appropriate staging work-up for children with melanoma have not been established Chest X-ray and abdominal ultrasound are recommended for all patients. Chest and abdominal computed tomography (CT) scan, technetium bone scan, and positron emission tomography (PET) could be suggested in case of thicker lesions or according to the physician's decision
Pathological assessment	Histological diagnosis should provide: the thickness of the tumor according to the Clark level and Breslow microstaging (expressed in millimeter), pleomorphism, mitoses/mm^2 and deep mitoses, lymphatic/vascular invasion, perineural diffusion. tumor type, type of growth phase, presence of microscopic satellites, presence of regression, presence of ulceration, tumor infiltrating lymphocytes (TIL), state of resection margins Sentinel node biopsy in staging regional lymph nodes, to establish whether elective node dissection is warranted, is recommended in high-risk cases (thickness > 0.75–1 mm or increased mitotic rate, evidence of ulceration, lymphovascular invasion)
Staging systems	TNM AJCC system
General treatment guidelines	Therapeutic recommendations for childhood melanoma should remain the same as for adults Need for referral to prime oncology center with expert physicians professionally dedicated to the management of this cancer in adults (or strict collaboration with them)
– Surgery	If the diagnosis of melanoma is confirmed at biopsy, a reexcision could be performed (at least 1 cm of surgical margin or according to tumor dimension) If the sentinel node is positive, patients should be offered a complete lymph node dissection
– Radiotherapy	No indication in localized disease Palliative role in metastatic disease
– Systemic treatment	High-dose interferon α-2b or interferon plus chemotherapy in case of regionally advanced disease or metastatic disease

dacarbazine-based chemotherapy has similar limited efficacy. The use of interleukin-2 has been studied in limited numbers, and although tolerable, its efficacy has not been assessed (Ribeiro et al. 1993; Bauer et al. 1995). Newer therapies, such as ipilimumab and the BRAF inhibitor PLX4032, have produced promising responses in adults with metastatic melanoma, but its use in pediatrics has not yet been studied (Flaherty et al. 2010; Hodi et al. 2010).

43.2.8 Survival Prognosis

The population-based analysis from the SEER reported a 5-year melanoma-specific survival of 93.6% (Strouse et al. 2005), which is consistent with European population-based data (80%) (Conti et al. 2001). This result is better than those reported in published hospital-based series (that can be biased by the selection of patients with more advanced disease) and however is better than that usually achieved in adults. Data from the SEER registry showed a 4% survival improvement per year during the last three decades. Other series have described slightly better outcomes in children than in adults (Ferrari et al. 2005; Saenz et al. 1999; Gibbs et al. 2000; Barnhill et al. 1995; Hamre et al. 2002; Schmid-Wendtner et al. 2002).

Overall survival rates for childhood melanoma are in excess of 95% for localized disease, around 70% for regional disease, while for metastatic cases, survival rates range from 10% to 50% (Lange et al. 2007) (Figs. 43.10–43.14).

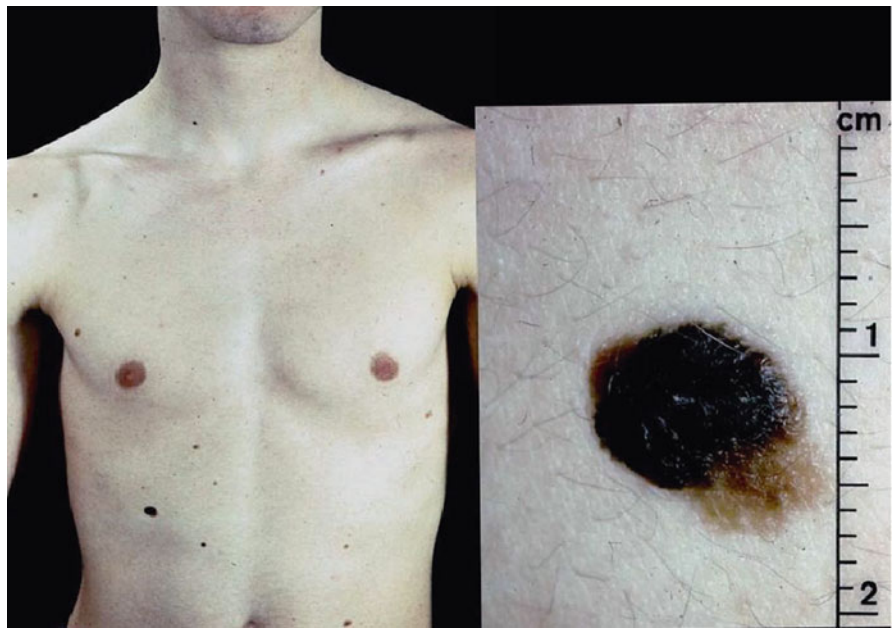

Fig. 43.10 Superficial spreading melanoma in a 17-year-old boy

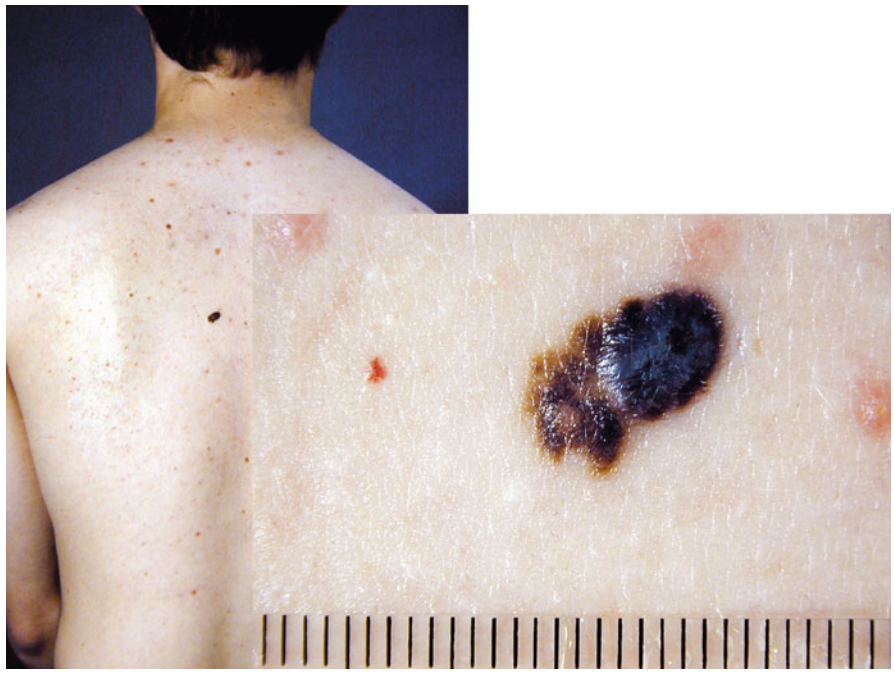

Fig. 43.11 Superficial spreading melanoma in a 18-year-old boy

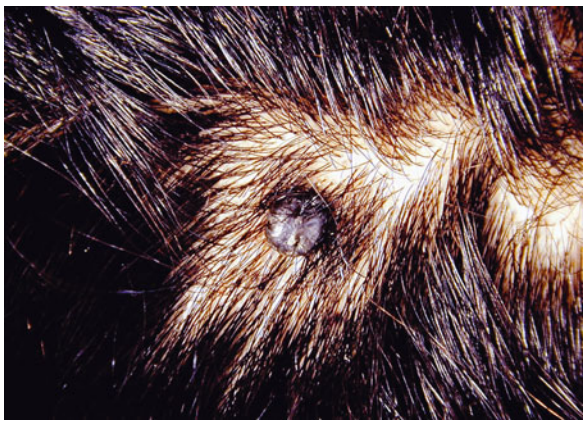

Fig. 43.12 Nodular melanoma in a 17-year-old girl

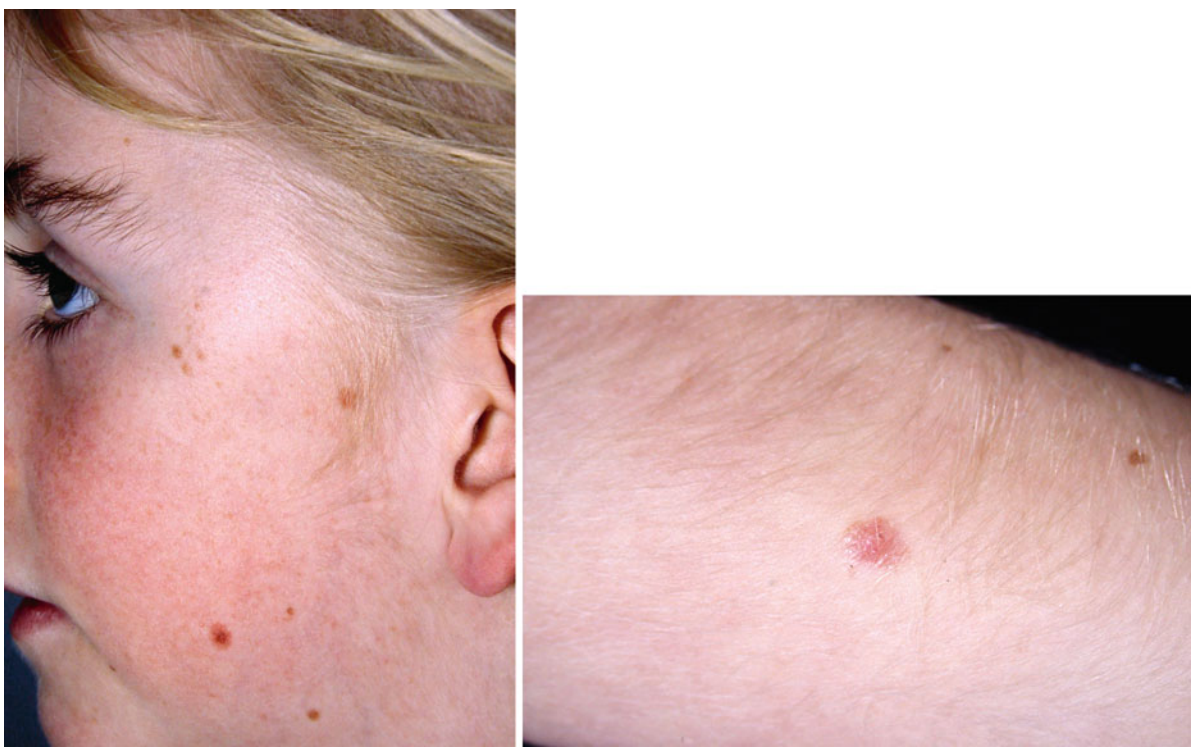

Fig. 43.13 Spitz nevus initially classified as malignant melanoma

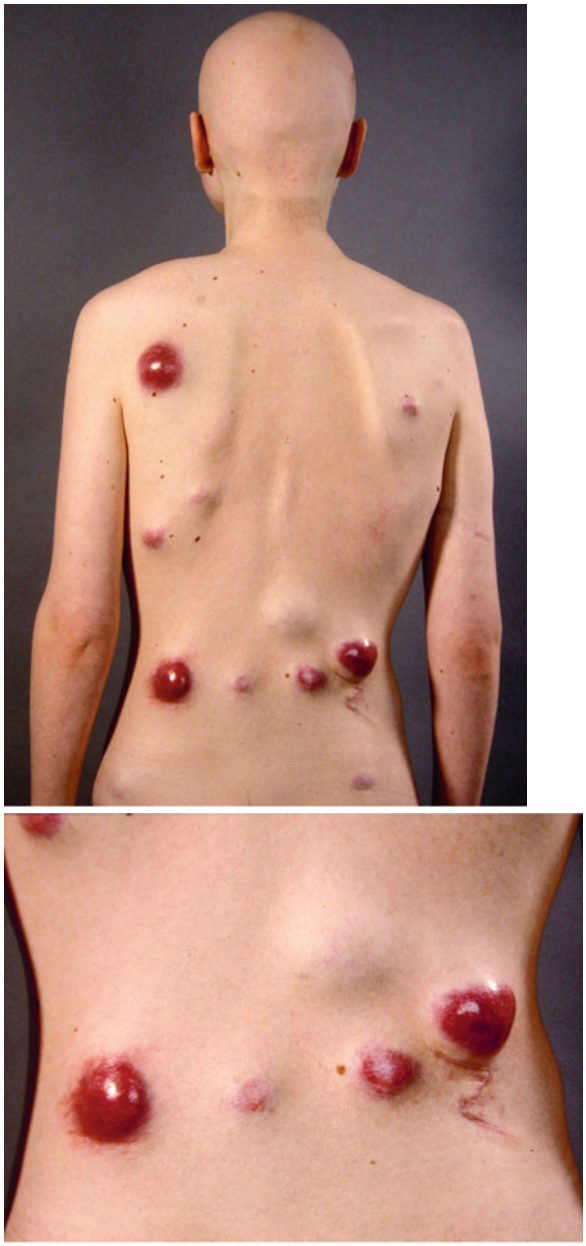

Fig. 43.14 Melanoma in a 15-year-old girl, distant metastases 14 months after diagnosis

43.3 Skin Carcinoma

Thomas K. Eigentler and Claus Garbe

Squamous cell carcinoma of the skin (SCC) is rarely diagnosed in childhood and adolescence. It is a malignant locally destructive epithelial tumor developing from the keratinocytes of the skin, which uncommonly metastasizes in nonimmunosuppressed patients.

Most cases are described in children suffering from xeroderma pigmentosum, an autosomal recessive disorder with mutations in the nucleotide excision repair complementation groups, resulting in extreme photosensitivity to ultraviolet radiation. It affects boys and girls in equal frequencies. In a series of 830 published cases, 45% of the patients had basal cell carcinoma or SCC. The median age of first nonmelanoma skin cancer among these patients was 8 years (Kraemer et al. 1987).

Another risk factor for developing SCC is iatrogenic chronic immunosuppression, e.g., after solid organ transplantation, whereas the risk of posttransplant cutaneous SCC is related to the kind of immunosuppression (especially cyclosporine), the duration of the immunosuppressive therapy, and the amount of cumulative UV exposure (Jensen et al. 1999). Also, sporadic chronic immunosuppression, e.g., in case of AIDS, is a risk factor for the development of SCC (Godfrey et al. 2003).

SCC is also reported to develop in children with interferon-gamma receptor two deficiency (Toyoda et al. 2010), in patients suffering from dystrophic epidermolysis bullosa (DEB), a genodermatosis resulting from mutations in COL7A1 and encoding type VII collagen (Horn and Tidman 2002), and in children with systemic sclerosis or pansclerotic morphea (Wollina et al. 2002) or chronic infections and wounds (Kassi et al. 2010). Single cases of a SCC arising in a nevus sebaceous of Jadassohn were also reported in the literature (Ball et al. 2005).

Treatment of choice is the complete excision of the tumor with three-dimensional histological visualization and evaluation of excision margins (Moehrle et al. 2007). In selected cases (deep infiltrating tumors), a sentinel node biopsy can be applied.

43.4 Other Rare Tumors of the Skin and Subcutaneous Tissue

Alberto Pappo and Andrea Ferrari

43.4.1 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a fibrohistiocytic tumor of intermediate malignancy that accounts for about 1–2% of all soft tissue sarcomas and most commonly affects young adults (McArthur 2007; Terrier-Lacombe et al. 2003). This malignancy has been described in children and can be congenital (Checketts et al. 2000; Chien et al. 2007; Jafarian et al. 2008; Pappo et al. 1997). In one series, pediatric DFSP accounted for 6% of all of this diagnosis seen at a single institution (McKee and Fletcher 1991). This tumor most commonly affects males and typically arises in the trunk and extremities. DFSP usually presents as a slow growing vascular-appearing macule or plaque that later develops into a nodular cutaneous mass. In a review of over 25 pediatric DFSP, the median age at presentation was 12 years. In another review of over 150 cases of pediatric DFSP, the most common sites of involvement were the trunk and extremities; the former location is preferentially seen in patients with congenital DFSP (Checketts et al. 2000; Chien et al. 2007; Jafarian et al. 2008; Pappo et al. 1997). Histologically, this tumor is characterized by a monotonous proliferation of fibroblasts arranged in a storiform pattern. A small number of DFSP have sarcomatous changes, a feature that has rarely been reported in the pediatric literature but that has been reported to carry an increased risk for the development of local recurrence and distant metastases (Abbott et al. 2006; Mentzel et al. 1998). DFSP is characterized by a common translocation t (17;22)(q22;q13) which fuses the *COL1A1* and *PDGFB* genes (McArthur 2007). This fusion protein is processed to a mature PDGFB and interacts with the PDGFB receptor present on the cell surface of DFSP in an autocrine or paracrine fashion (Rubin et al. 2002). The primary treatment of DFSP is wide surgical resection with negative margins (Fiore et al. 2005); Mohs micrographic surgery has also been used in selected cases (Sondak et al. 1999). Using this primary surgical approach, cause-specific mortality in adults has been reported to be 3% in 10 years, and local recurrence rates have been documented in less than 5% of cases (Fiore et al. 2005). For adults and children with unresectable or metastatic DFSP, the administration of imatinib mesylate has produced promising clinical responses (Rutkowski et al. 2010; Price et al. 2005; Gooskens et al. 2010).

43.4.2 Giant Cell Fibroblastoma

Giant cell fibroblastoma (GCF) is a rare nonmetastasizing subcutaneous fibrohistiocytic neoplasm that occurs predominately in younger patients. In one series of 86 GCF, the median age was 6 years, and nearly two thirds of the patients were younger than 10 years of age. This tumor most commonly presents as painless mass located in the dermis or subcutis and most commonly arises in the trunk. GCF has been referred as a juvenile form of DFSP, and both entities share the t (17;22)(q22;q13) (Jha et al. 2007). Histologically, GCF is characterized by the presence of spindle cells that infiltrate adnexal structures and form pseudovascular spaces that are lined with discontinuous multinucleated giant tumor cells (Billings and Folpe 2004) Although both GCF and DFSP have similar cytogenetic findings, adult DFSP is often characterized by the presence of ring chromosomes, a feature that is notably absent in pediatric DFSP and GCF. The clinical behavior of GCF is similar to DFSP, and surgical resection with negative margins is the treatment of choice.

43.4.3 Angiomatoid Fibrous Histiocytoma

Angiomatoid fibrous histiocytoma (AFH) is a rare subcutaneous fibrohistiocytic tumor of intermediate malignancy that accounts for about 0.3% of all soft tissue sarcomas (Thway 2008). AFH was initially described by Enzinger in 1979 as a soft tissue tumor related to malignant fibrous histiocytoma that affected the superficial tissues of younger patients (Enzinger 1979). More recent studies have demonstrated that this entity has an excellent prognosis following surgical resection alone, and thus the original nomenclature of "malignant" has been removed from its name (Thway 2008). In one series of 108 patients, the median age at presentation was 14 years, females were slightly more commonly affected, and the tumor most commonly arose in the extremities (65%) and trunk (28%) (Costa and Weiss 1990). These

tumors have an indolent clinical presentation, and most are located superficially; in one series, 60% of tumors arose within areas of normal lymphoid tissue (Fanburg-Smith and Miettinen 1999; Antonescu et al. 2007). In one series, systemic symptoms, such as anemia, weight loss, and fever, were seen in 14%, 4%, and 2% of patients (Fanburg-Smith and Miettinen 1999). Histologically, AFH is characterized by the presence of a fibrous pseudocapsule, a round or spindled histiocyte-like proliferation of cells, a plasma lymphocytic response, and pseudovascular spaces (Antonescu et al. 2007). Cytogenetic studies have documented translocations involving the *FUS* gene on chromosome 12q13 with either the *EWSR1* gene on chromosome 22q12 or the *FUS* on 16p11. More recently, a translocation between *EWSR1* and *CREB1* on chromosome 2q34 has been identified as the predominant fusion product in AFH. The treatment of choice for this tumor is complete surgical excision. Local recurrences have been reported to occur in up to 12% of patients after incomplete excision, but reexcision often renders patients disease-free. In one series, 85 of 86 patients were alive and disease-free, and only one patient developed nodal metastases. In another series, only 1 of 94 patients developed distant metastases (Fanburg-Smith and Miettinen 1999; Antonescu et al. 2007).

43.4.4 Plexiform Fibrohistiocytic Tumor

Plexiform fibrohistiocytic tumor is a rare neoplasm with features that resemble fibrous histiocytoma and fibromatosis and mainly affects children and young adults. The median age at diagnosis in two large series was 14.5 and 20 years, respectively (Moosavi et al. 2007; Enzinger and Zhang 1988). This tumor occurs slightly more often in females and presents as a painless slow growing nodule located in the dermis or subcutis (Luzar and Calonje 2010). The tumor most often involves the upper extremity, with the fingers, hands, and the wrist being more commonly affected (Taher and Pushpanathan 2007). The lesions are usually small and contain a mixture of histiocyte-like and spindle fibroblast-like cells. On low-power microscopy, the dermis and subcutaneous tissue are infiltrated with multiple nodules that contain multinucleated osteoclast-like giant cells (Luzar and Calonje 2010). Immunocytochemistry reveals CD68 positivity on the histiocyte and osteoclast-like cells, whereas the fibroblast-like cells show focal positivity for smooth muscle actin. Cytogenetic analysis in two cases has revealed numerous deletions and a 46,XY,t(4;15)(q21;q15) translocation (Luzar and Calonje 2010). Surgical excision is the treatment of choice, but local recurrences have been documented in up 40% of cases within the first 2 years from diagnosis. Recurrences are usually successfully treated with surgical reexcision. Metastases to lymph nodes and lung have been rarely described (Salomao and Nascimento 1997).

43.4.5 Dermoid Cysts

Dermoid cysts are a subset of benign heterotopic neoplasms termed choristomas, probably deriving from dermal and epidermal tissues trapped in the cranial fusion lines as the neural tube closes in embryogenesis. Histologically, they may have a lining of squamous epithelium with dermal elements, such as hair follicles, sebaceous, and sweat glands: within the cyst, mature skin complete with hair follicles and sweat glands, sometimes clumps of long hair, and often pockets of sebum, blood, fat, bone, nails, teeth, eyes, cartilage, and thyroid tissue can be found.

Dermoid cysts can be deep and superficial (the former being more frequent in teenagers; the latter, in early childhood) and may occur as soft tissue swelling in three primary locations in the head and neck: the frontotemporal region, the periorbital region, and the nasoglabellar region.

Complete surgical excision – preferably in one piece and without any spillage of cyst contents – is curative, but dermoid cysts can recur if not completely excised. Lesions invading deeply within the orbit may require a more aggressive approach. Craniotomy and neurosurgical involvement may be required for intracranial extension (Ahuja and Azar 2006; Bartlett et al. 1993; Pryor et al. 2005).

43.5 Vascular Tumors

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Vascular tumors are the most common subcutaneous neoplasms in children. The tumor cells in vascular tumor are the endothelial cells that show dedifferentiation, transformation, and uncontrolled growth, leading to a benign or malignant neoplastic phenotype. Genetic alterations as well as molecular biological characteristics are responsible here for, but in most vascular tumor types this is yet not clear. The pathogenesis of vascular tumor and the possible role of genetic alterations are still unclear.

The most frequent vascular tumor in childhood is *infantile hemangioma* (IH), which shows a special biology with continuous growth during the first year of life but spontaneous regression thereafter. Cutaneous IH are very frequent. Variants of IH have been described, from capillary IH and cavernous to segmental and congenital IH. IH may arise anywhere, but the head and neck region is the most frequent location. IH are connected to the circulatory system and filled with blood. Clinically, superficial IH appears as a cutaneous lesion or a bluish-red, rubbery or firm, well-circumscribed mass (Coffin and Dehner 1993). Clinical complications are related to ulceration and hemorrhages, or in case of impingement upon vital structures, as larynx or mediastinum. In most cases, IH hemangiomas will disappear over time; however, treatment is required when the tumor interferes with vision and breathing or threatens significant cosmetic injury (Haggstrom et al. 2006). Different treatment approaches have been proposed over the years, i.e., surgery, oral corticosteroids, injection of corticosteroid directly into the lesion, pulsed dye laser (Rizzo et al. 2009), and systemic therapy with interferon and vincristine (Wilson et al. 2007). A recent and extremely promising treatment option is represented by beta-blocker propranolol (Léauté-Labrèze et al. 2008).

IH can easily be confounded with other benign vascular tumors, such as tufted angioma or kaposiform hemangioendothelioma. However, in contrast to IH, they do not show spontaneous regression. In most cases, only clinical evolution or histology can discriminate these benign vascular tumors from IH.

Table 43.3 Classification of vascular anomalies

Vascular tumors (benign)	Vascular malformations
Infantile hemangioma (IH)	Capillary malformations
Congenital hemangioma (ICH): rapid involuting (RICH) or noninvoluting (NICH)	Port-wine stain, telangiectasia, angiokeratoma
Tufted angioma (TA) with or without Kasabach–Merritt phenomena	Venous malformation Glomangioma (glomuvenous malformation) Familial cutaneous and mucosal venous malformation (CMCV)
Kaposiform hemangioendothelioma (KHE) with or without Kasabach–Merritt phenomena	Lymph vessel malformation Lymphangioma
Epithelioid hemangioendothelioma (EH)	Arterial malformation
Other hemangioendothelioma	Combined vascular malformation
Spindle cell, retiform, polymorphous, etc. Dermatological acquired vascular tumors Pyogenic granuloma (PG), etc.	AV malformation, etc.

On the other side of the spectrum, malignant vascular tumors are extremely rare and show aggressive behavior.

Latest basic research achievements have opened the possibility to discriminate between blood and lymph vessels: blood and lymph endothelial cells show special biological characteristics. Most of the vascular tumors are formed by blood endothelial cells; only rarely, lymph vessels can be found. In fact, most *lymphangiomas* are really malformations that arise from lymphatic tissue sequestered during embryologic development. However, some are probably true neoplasms with invasive growth pattern. In the future, these two vessel systems will be further characterized in more detail in vascular tumors, as it has already been the case in vascular malformations. The classification of the International Society on the Studies of Vascular Anomalies (ISSVA) for vascular anomalies clearly separates vascular tumors from vascular malformations that are inborn defects of vasculogenesis (Table 43.3).

43.5.1 Infantile Hepatic Hemangiomas

Infantile hepatic hemangiomas (IHH) can be found in the context of disseminated or diffuse neonatal *hemangiomatosis* that is characterized by multiple cutaneous IH, usually of small size, associated with visceral involvement. IHH are classified into three categories: focal, multifocal, or diffuse, according to the number of lesions. The clinical presentation can be asymptomatic or associated with hepatomegaly, jaundice, or liver dysfunction. Ultrasound or magnetic resonance imaging (MRI) can identify the vascular tumors with increased perfusion in the duplex ultrasound and hyperintensive signals in T2 (Fig. 43.15). Diffuse IHH can be life-threatening since they may induce congestive heart failure associated with high-volume vascular shunting. Hypothyroidism secondary to overproduction of type III iodothyronine deiodinase may be present.

Severe and complicated IHH require therapy. First-line therapy of IHH with hemodynamically significant shunting used to be administration of systemic corticosteroids. However, recently, dramatically clinical improvement and decrease in size of IHH on propranolol were reported. This new therapeutic option may replace embolization; other pharmacological agents, such as vincristine and alfa-2a interferon; hepatic artery ligation; resection; or liver transplantation that have been reported in literature before (Léauté-Labrèze et al. 2008; Mazereeuw-Hautier et al. 2010; Marsciani et al. 2010).

43.5.2 Pyogenic Granuloma

Pyogenic granuloma (PG) is a benign nonneoplastic mucocutaneous lesion. It is usually a small red, oozing, and bleeding bump (Fig. 43.16). PG can result to constant minor trauma and might be related to hormonal changes. PG preferentially affects the gingiva but may also occur on the lips, tongue, cheek or oral mucosa, and palate. In the mouth, PG is manifested as a sessile or pedunculated, resilient, erythematous, exophytic, and painful papule or nodule with a smooth or lobulated surface that bleeds easily. The most common treatment is surgical excision or combinations of curettage, shave, and cautery (Tay et al. 1997; Matsumoto et al. 2001; Giblin et al. 2007).

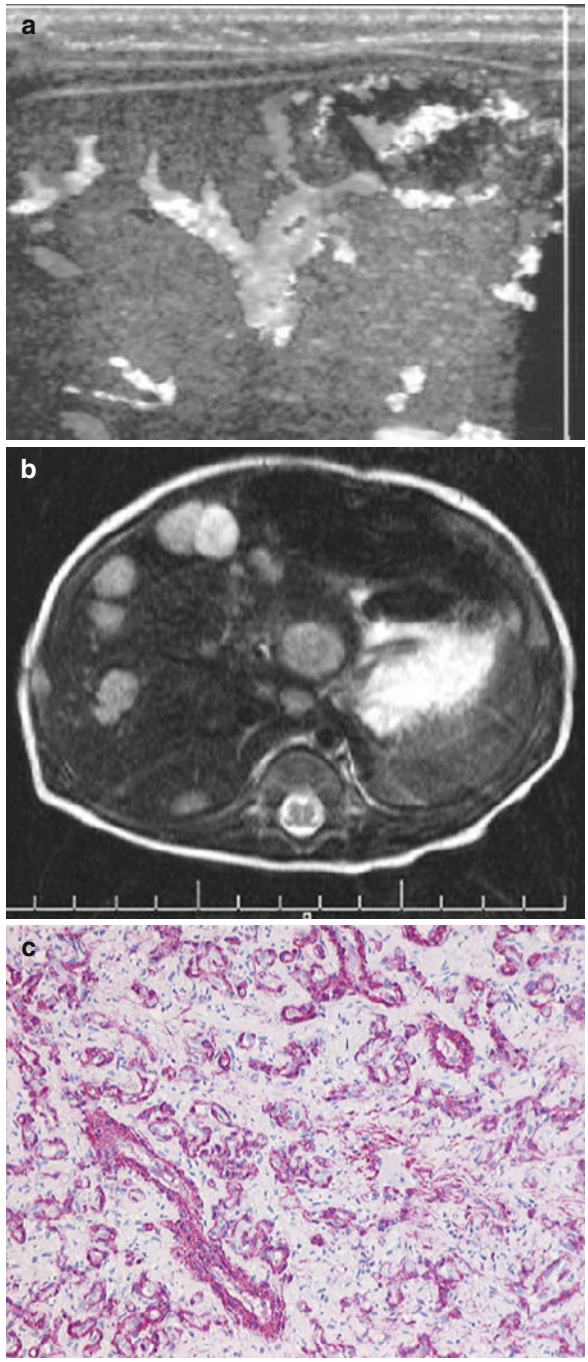

Fig. 43.15 Infantile hepatic hemangiomas in a newborn child with numerous skin hemangiomas. (**a**) Duplex ultrasound detects multiple hepatic lesions with perfusion signal. (**b**) In T2-weighted MRI, the lesions are hyperintense. (**c**) Shows an immunohistological staining of a biopsy with alpha-actin antibodies. Multiple blood vessels are seen, confirming the diagnosis of infantile hepatic hemangiomas

43.5.3 Tufted Angioma

Tufted angiomas (TA) are rare locally aggressive vascular tumors of unknown pathogenesis. Most appear during childhood: approximately 25% of cases are congenital, and 50% appear in the first year of life. TA that are present at birth (congenital TA) or in the first year of life (acquired TA) have a greater tendency to spontaneously regress than those that appear later in life (Alberola et al. 2010). The clinical presentation of TA is nonspecific and characterized by bluish-erythematous plaques (Fig. 43.17a) or nodules. There is a well-recognized association with the Kasabach–Merritt phenomenon. The differential diagnosis includes IH, KHE, and vascular malformations.

TA have a characteristic histology consisting of a proliferation of endothelial cells forming lobules with the typical "shotgun" distribution. TA are considered neoplasms of intermediate malignancy because of infiltrative growth, local aggressiveness, and variable prognosis. To date, definitive treatment for TA has had limited success. Local treatment with laser (Fig. 43.17b) and steroids, vincristine, or experimental antiangiogenic drugs has been reported (Fahrtash et al. 2010).

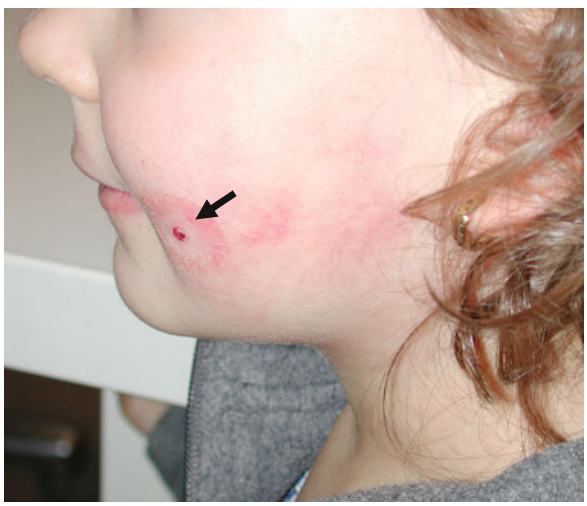

Fig. 43.16 Pyogenic granuloma at the cheek of a 4-year-old girl. The reddish nodule developed in the last 4 weeks and shows intermitted bleeding

43.5.4 Kaposiform Hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is a locally aggressive, immature vascular neoplasm typically presenting in infancy and the first decade. KHE may involve various organs: generally, it originates on the skin, affecting deeper tissue by infiltrative growth (Fig. 43.18), and the retroperitoneum. KHE tend to be locally invasive but are not known to produce distant metastases. Visceral involvement is uncommon, but several cases with bone, retroperitoneal, mediastinal, or choledochus involvement have been described (Terui et al. 2010). KHE appears as one or multiple masses and may involve the underlying bone and rarely regional lymph nodes. There is no known association with HIV or HHV 8 infection. In most cases, KHE can be associated to the Kasabach–Merritt phenomena. The development of KHE in adolescents or in adults is very rare, but cases have also been described.

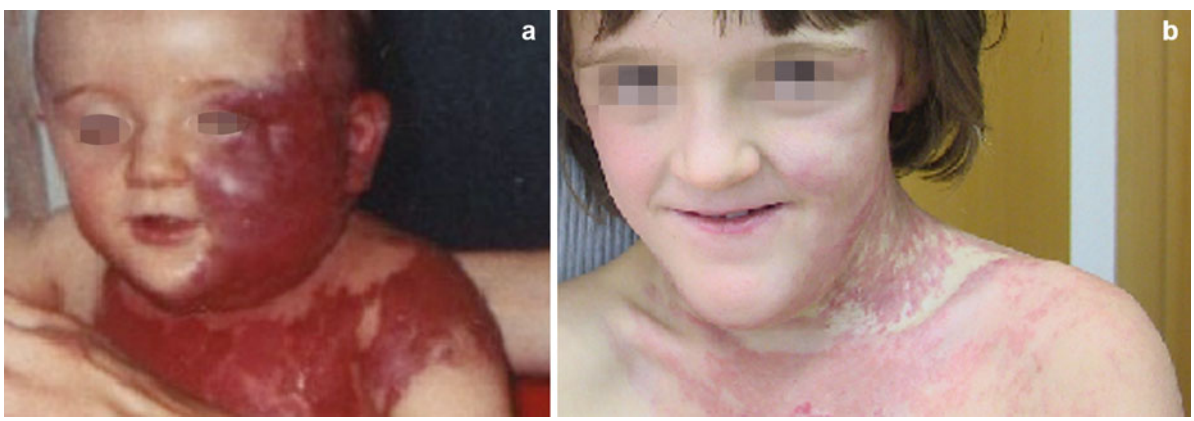

Fig. 43.17 (**a**) Tufted angioma in a 1-year-old girl. The red lesion showed continuous growth during the first year of life. A biopsy confirmed the diagnosis of tufted angioma. After birth, an accompanying Kasabach–Merritt phenomenon was treated by corticosteroids. (**b**) Laser therapy led to brightening of the vascular tumor

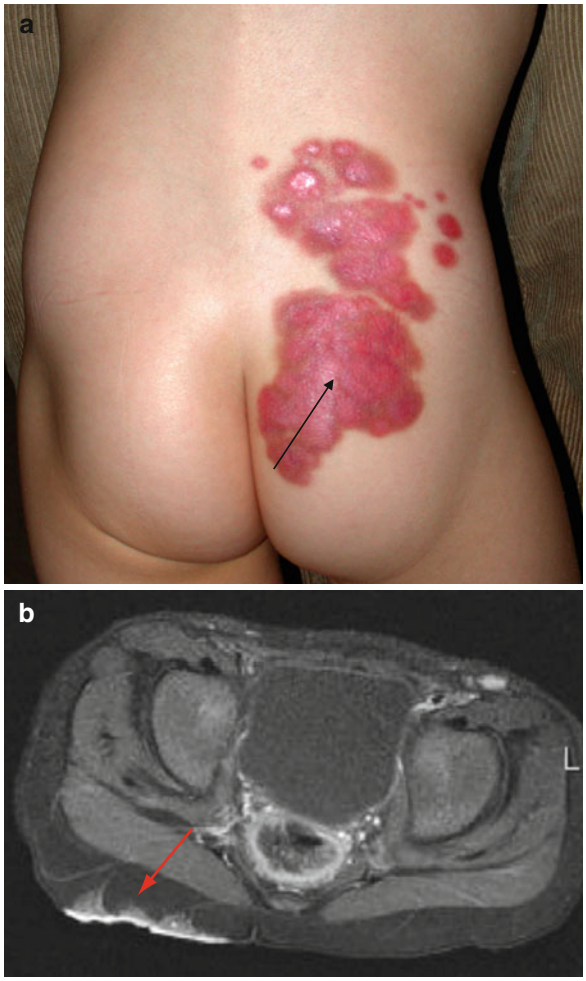

Fig. 43.18 (**a**) Kaposiform hemangioendothelioma at the lumbosacral region. (**b**) Infiltrative growth in the subcutaneous region has been confirmed by MRI

Microscopically, KHE is characterized by nodules containing fascicles of spindle cells interspersed among small vessels blending with slit-like vascular spaces. Glomeruloid nests of endothelial cells are found at the periphery. Fibrous bands surround nodules and contain dilated lymphatic vessels. Small biopsies, including capillary blood vessel biopsy, may mimic a capillary hemangioma. The spindle cells are usually nonreactive for factor VIII–related antigen and stain for smooth muscle actin. Endothelial markers CD31 and CD34 are expressed in the capillary vessels. GLUT-1, expressed in infantile hemangioma, is typically negative.

Gradual regression of KHE has been observed. However, the tumor can cause potentially life-threatening complications. Several factors are associated with the outcome of patients with KHE: accessibility to surgical excision, location (cutaneous versus visceral), size of tumoral mass, and the Kasabach–Merritt phenomena. Death related to the Kasabach–Merritt syndrome or to the progressive failure of the infiltrated organ(s) has been described. Huge visceral tumor may lead to a 40–50% mortality rate. Various therapeutic options have been recommended according to the site, extent, and behavior of the disease: steroid, interferon-alpha, and vincristine – also in combination – are often used (Fahrtash et al. 2010).

43.5.5 Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EH) was first described by Weiss and Enzinger in 1982 (Weiss and Enzinger 1982). It is a vascular tumor occurring at any age and may be either superficially or deeply located, arising at a variety of sites, including the skin and subcutis, the skeleton (Fig. 43.19), the lung, liver, and central nervous system. Microscopically, it arises from a vessel and extends into the surrounding soft tissue. The tumor is composed of epithelioid endothelial cells arranged in short cords or solid nests, with a prominent myxoid–jaline matrix. The diagnostic key feature is represented by epithelioid cells with a cytoplasmic vacuole representing a miniature lumen. It shows positive staining for endothelial markers (CD31, CD34) and cytokeratin.

EH of the liver may have peculiar features at enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, i.e., nodular lesions with a tendency to coalesce, with a peculiar target appearance due to the presence of a central sclerotic zone and a peripheral region of cellular proliferation with high signal intensity; a lollipop sign given by a hepatic or portal vein terminating at or just within the periphery of some of the liver lesions has been described (Scoazec et al. 1988; Lyburn et al. 2003; Kehagias et al. 2000; Alomari 2006).

According to WHO, EH is a malignant vascular tumor because of its high metastatic rate. Metastases to regional lymph nodes, lung, liver, and bone occur in 30% of cases but cause death in half of the patients affected. Cellular atypia, mitotic activity (>1/10 HPF), necrosis, or diffuse spindle cell morphology appear to be associated with metastases (Mentzel et al. 1997). Complete local excision – if possible – is the preferred therapeutic measure. If impossible, sarcoma-based

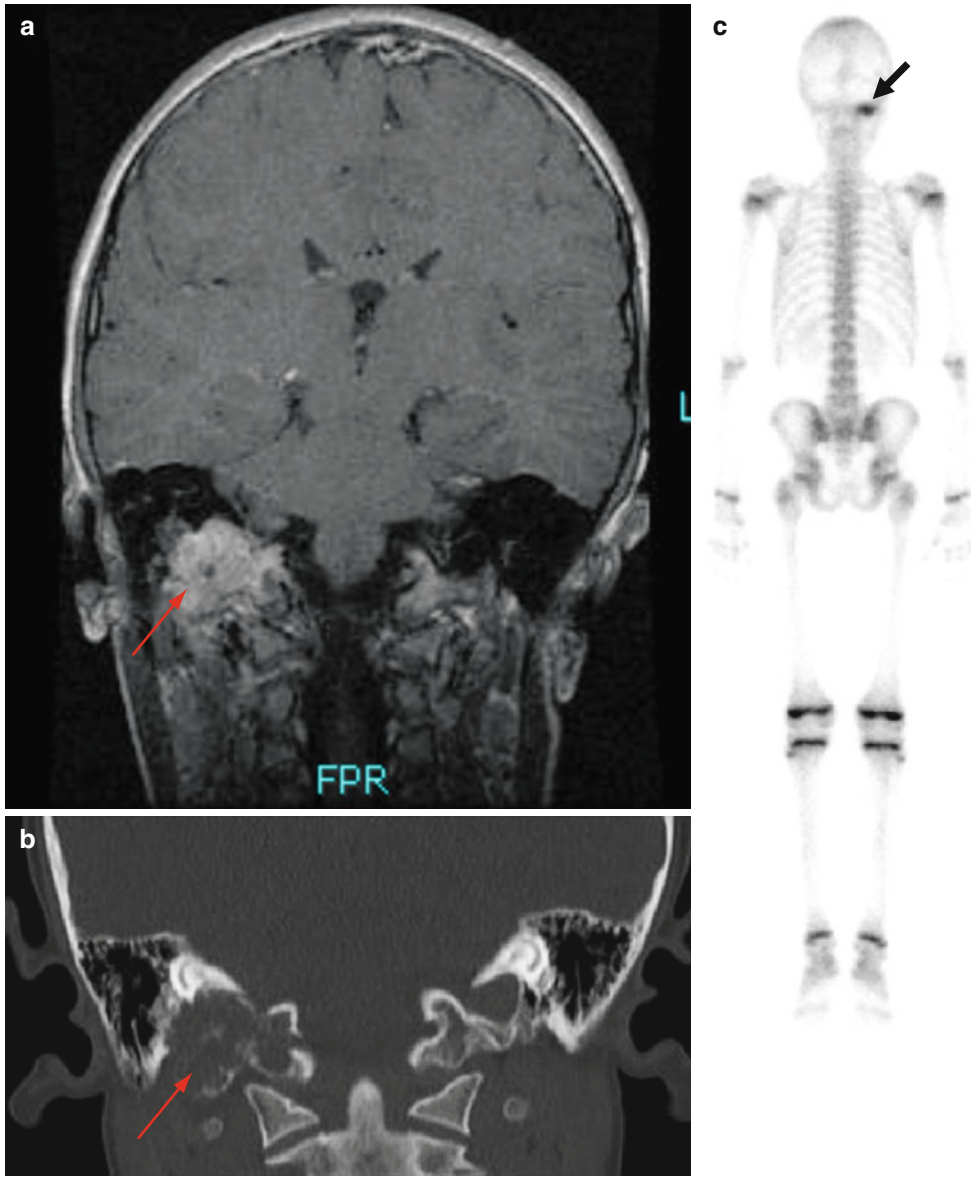

Fig. 43.19 (**a**) Epithelioid hemangioendothelioma at the right petrosal bone in a 12-year-old boy who presented with facial nerve paresis on the right side. A biopsy confirmed the diagnosis. (**b**) Signs of skeletal destruction at the CT scan. (**c**) Early phase of technetium-99 m scintigraphy showing a unifocal lesion at the right petrosal bone

chemotherapy or alpha-2a-interferon is administered (Ferrari et al. 2001). In particular, alpha-2a-interferon is potent inhibitor of angiogenesis and acts by blocking the action of fibroblast growth factor. Many tumors of vascular origin, including EH, are characterized by endothelial cell migration and proliferation in the proliferative phase, and the major stimulus for this proliferation is fibroblast growth factor. The role of alpha-2a-interferon is of particular interest because its mechanism of action is the inhibition of this stimulus (Isowa et al. 2002; Kumar et al. 2003; Roudier-Pujol et al. 1994; Calabrò et al. 2007). Few data are available on the role of radiotherapy for inoperable EH. EH of the liver is characterized by an unpredictable prognosis: in younger patients, a wait-and-see strategy is usually adopted. Orthotopic liver transplantation may be considered, even in the presence of limited extrahepatic disease (Kelleher et al. 1989; Madariaga et al. 1995).

43.5.6 Kaposi Sarcoma

Kaposi sarcoma is rarely diagnosed in childhood and adolescence in general. It is a locally aggressive vascular neoplasm caused by the human herpesvirus 8 (HHV-8), which can be classified into four different types: classic, iatrogenic (immunosuppression-associated), AIDS-associated, and African/endemic. The classic type predominantly affects older adults of Mediterranean or Eastern European ancestry. Only single cases have been reported in children (Byun et al. 2010; Sahin et al. 2010). The iatrogenic type is linked to immunosuppression (e.g., after solid organ transplantation) and normally resolves with immune restoration. In a series of 326 organ-transplanted pediatric patients, 6 children developed a Kaposi sarcoma (Penn 1994). In contrast to the classic form of Kaposi sarcoma which is mainly located at the extremities, AIDS-associated Kaposi sarcoma usually develops on the head, back, neck, muscular palate, and the area of the gingiva and is seen in patients with low CD4-T-lymphocytes (<400/μL). Typically, Kaposi sarcoma presents with cutaneous lesions in the form of plaques, patches, or nodules. In the classic type, purplish, reddish-blue, or dark-brown macules that can ulcerate are found. In rare cases, internal organs can be affected as well as lymph nodes. In histopathology, the patch stage and the plaque, as well as the nodular stage, can be described. A vascular proliferation is seen with endothelial cells lining perivascular spaces, and new blood vessels can be produced in the lumen of preexisting blood vessels.

In a US series of 4,954 children with AIDS, 8 developed an AIDS-associated Kaposi sarcoma (Biggar et al. 2000). In patients with AIDS-associated Kaposi sarcoma, a highly active antiretroviral therapy (HAART) has been shown to prevent or induce regression of Kaposi sarcoma. Finally, the African/endemic type can be differentiated into the cutaneous and lymphadenopathic type and is seen in pediatric populations in Africa, most of whom develop the clinical disease as a consequence of HIV infection (Ziegler and Katongole-Mbidde 1996).

As most cases of Kaposi sarcoma in children appear in relation to immunosuppression, the major goal in the treatment is to restore immune competence either by changing the immunosuppressant scheme in organ-transplanted children (e.g., to mTOR inhibitors) (Yuksekkaya et al. 2009) or by applying an antiviral therapy in case of HIV infection. Children suffering from the classical type of Kaposi sarcoma can be treated locally by surgery (in case of small single lesions), radiation, or systemic interferon-alpha. Chemotherapy using liposomal anthracyclines, bleomycin, and vincristine is used (Tulpule et al. 1998).

43.5.7 Angiosarcoma

Angiosarcomas (AS) typically affect adult and elderly patients (it accounts for 1% of all adult soft tissue sarcomas) (Penel et al. 2010) and are extremely rare in children, representing less than 0.3% of pediatric sarcomas overall. Only two series have been reported in pediatric age, respectively, including 15 (Deyrup et al. 2006) and 12 patients (Ferrari et al. 2002).

Histology shows vascular structures with an infiltrative growth pattern and more solid areas with sheets and nests of malignant endothelial cells frequently displaying an epithelioid morphology. Spindled areas can be present as well. Necrosis is found in more than 80% of cases. Tumor cells express CD31 and CD34.

In adults, the majority of AS develop as cutaneous tumors. In children, the majority of AS arise in mediastinum and heart but may involve also visceral organs, breast, and deep soft tissue of abdomen or pelvis. Two risk factors are well established: chronic lymphoedema and previous radiotherapy. Clinical presentations of AS are heterogeneous. Possible output cardiac failure can result in very young patients due to arteriovenous shunting. The lesions can appear as hemorrhagic masses. Hepatic AS are extremely rare and usually present with a rapidly enlarging liver. By the time they are diagnosed, the lesion is often unresectable. AS are highly aggressive tumors; metastases are common, frequently to the lung. The mortality rate is generally high, particularly in hepatic AS in which death usually occurs within the first 6 months. In childhood, published series reported a mortality rate ranging between 62% and 65%.

Large resection followed, if possible, by adjuvant radiotherapy is the cornerstone of curative-intent treatment of localized AS. There are no convincing data supporting the administration of adjuvant chemotherapy, but most protocols currently require adjuvant chemotherapy in high-grade (as AS is) and large tumors, even when resected (see Chap. 44). For metastatic or locally advanced AS, doxorubicin-based

chemotherapy or chemotherapy based on weekly paclitaxel (Penel et al. 2008) seems to provide the longer progression-free survival. Three phase II or parts of phase II trials have been published in the last 2 years in adult setting, investigating weekly paclitaxel, sorafenib, and imatinib, demonstrating that clinical trials are feasible for such rare diseases. Biological evidences for the key role of angiogenetic factors have been accumulated during the last years and support the further investigation of antiangiogenetic agents alone and almost combination with chemotherapy in such disease.

43.5.8 Kasabach–Merritt Phenomenon

Kasabach–Merritt phenomenon (KMP) is defined as thrombocytopenia and hypofibrinogenemia with elevated fibrin split products (D-dimers), suggestive of an active consumptive coagulopathy. Thrombocytes are low, ranging from 6,000 to 98,000, with fibrinogen levels less than 100 mg/dL; whereas, D-dimers are elevated. Prothrombin times (PT) and activated partial thromboplastin time (PTT) can range from normal to significantly prolonged. Additionally, anemia can be present at diagnosis as a consequence of intravascular hemolysis, including red blood cell fragmentation, elevated LDH, and hyperbilirubinemia.

Successful treatment of the underlying vascular tumor is critical to the correction of KMP and to the overall survival of patients. Children with KMP can die of hemorrhage or invasion/compression of vital structures by the vascular tumor. Mortality has ranged from 10% to 30% in most series.

A curative therapy of KMP can only be achieved by treatment of the underlying vascular tumor. However, supportive care to maintain hemostasis is necessary. Platelet transfusions should be reserved for active bleeding or in preparation for surgery or procedures. Aminocaproic acid and local measures may be helpful to reduce the need for platelet transfusions. Antiplatelet agents, such as acetylsalicylic acid and dipyridamole, have been used to reduce platelet aggregation within the vascular tumor. Treatment of hypofibrinogenemia with cryoprecipitate and prolonged PT or PTT with fresh frozen plasma should be a clinical decision rather than correction of a laboratory result. Symptomatic anemia should be treated with red blood cell transfusions.

References

Abbott JJ, Oliveira AM, Nascimento AG (2006) The prognostic significance of fibrosarcomatous transformation in dermatofibrosarcoma protuberans. Am J Surg Pathol 30:436–443

Ahuja R, Azar NF (2006) Orbital dermoids in children. Semin Ophthalmol 21:207–211

Alberola FT, Betlloch I, Montero LC, Nortes IB, Martinez NL, Paz AM (2010) Congenital tufted angioma: case report and review of the literature. Dermatol Online J 16:2

Alexander A, Samlowski WE, Grossman D et al (2003) Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. J Clin Oncol 21:2179–2186

Alomari AI (2006) The lollipop sign: a new cross-sectional sign of hepatic epithelioid hemangioendothelioma. Eur J Radiol 59:460–464

Antonescu CR, Dal Cin P, Nafa K et al (2007) EWSR1-CREB1 is the predominant gene fusion in angiomatoid fibrous histiocytoma. Genes Chromosomes Cancer 46:1051–1060

Balch CM, Gershenwald JE, Soong SJ et al (2009) J Clin Oncol 27(36):6199–6206. Epub 2009 Nov 16

Ball EA, Hussain M, Moss AL (2005) Squamous cell carcinoma and basal cell carcinoma arising in a naevus sebaceous of Jadassohn: case report and literature review. Clin Exp Dermatol 30:259–260

Barnhill RL, Flotte TJ, Fleischli M, Perez-Atayede A (1995) Cutaneous melanoma and atypical Spitz tumors in childhood. Cancer 76:1833–1845

Bartlett SP, Lin KY, Grossman R, Katowitz J (1993) The surgical management of orbitofacial dermoids in the pediatric patient. Plast Reconstr Surg 91:1208–1215

Bastian BC, Wesselmann U, Pinkel D, Leboit PE (1999) Molecular cytogenetic analysis of Spitz nevi shows clear differences to melanoma. J Invest Dermatol 113: 1065–1069

Bastian BC, Kashani-Sabet M, Hamm H et al (2000) Gene amplifications characterize acral melanoma and permit the detection of occult tumor cells in the surrounding skin. Cancer Res 60:1968–1973

Bauer M, Reaman GH, Hank JA et al (1995) A phase II trial of human recombinant interleukin-2 administered as a 4-day continuous infusion for children with refractory neuroblastoma, non-Hodgkin's lymphoma, sarcoma, renal cell carcinoma, and malignant melanoma. A Childrens Cancer Group study. Cancer 75:2959–2965

Biggar RJ, Frisch M, Goedert JJ (2000) Risk of cancer in children with AIDS. AIDS-Cancer Match Registry Study Group. JAMA 284:205–209

Billings SD, Folpe AL (2004) Cutaneous and subcutaneous fibrohistiocytic tumors of intermediate malignancy: an update. Am J Dermatopathol 26:141–155

Bleyer AOLM, Barr R, Ries LA (2006) Cancer epidemiology in older adolescents and young adults 15 to 29 years of age including SEER incidence and survival: 1975–2000. National Cancer Institute, Bethesda

Bono A, Ferrari A (2005) Early diagnosis remains the most reliable way to cure children with melanoma. Pediatr Blood Cancer 45(3):355

Bono A, Maurichi A, Moglia D et al (2001) Clinical and dermatoscopic diagnosis of early amelanotic melanoma. Melanoma Res 11:491–494

Brenn T, McKee PHM (2008) Melanoma in children and adolescents. Diagn Histopathol 14:18–27

Brose MS, Volpe P, Feldman M et al (2002) BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res 62:6997–7000

Busam KJ, Murali R, Pulitzer M et al (2009) Atypical spitzoid melanocytic tumors with positive sentinel lymph nodes in children and teenagers, and comparison with histologically unambiguous and lethal melanomas. Am J Surg Pathol 33:1386–1395

Butter A, Hui T, Chapdelaine J et al (2005) Melanoma in children and the use of sentinel lymph node biopsy. J Pediatr Surg 40(5):797–800

Byun M, Abhyankar A, Lelarge V et al (2010) Whole-exome sequencing-based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma. J Exp Med 207: 2307–2312

Calabrò L, Di Giacomo AM, Altomonte M et al (2007) Primary hepatic epithelioid hemangioendothelioma progressively responsive to interferon-alpha: is there room for novel anti-angiogenetic treatments? J Exp Clin Cancer Res 26(1):145–150

Ceballos PI, Ruiz-Maldonado R, Mihm MC Jr (1995) Melanoma in children. N Engl J Med 332:656–662

Cerroni L, Barnhill R, Elder D et al (2010) Melanocytic tumors of uncertain malignant potential: results of a tutorial held at the XXIX symposium of the international society of dermatopathology in Graz, October 2008. Am J Surg Pathol 34:314–326

Chao MM, Schwartz JL, Wechsler DS, Thornburg CD, Griffith KA, Williams JA (2005) High-risk surgically resected pediatric melanoma and adjuvant interferon therapy. Pediatr Blood Cancer 44:441–448

Checketts SR, Hamilton TK, Baughman RD (2000) Congenital and childhood dermatofibrosarcoma protuberans: a case report and review of the literature. J Am Acad Dermatol 42:907–913

Chien CR, Chang YL, Lin DT, Yang RS (2007) Excellent survival of pediatric dermatofibrosarcoma protuberans in Taiwanese. Pediatr Surg Int 23:211–214

Coffin CM, Dehner LP (1993) Vascular tumors in children and adolescents: a clinicopathological study of 228 tumors in 222 patients. Pathol Annu 1:97–120

Conti EMS, Cercato MC, Gatta G et al (2001) Childhood melanoma in Europe since 1978: a population-based survival study. Eur J Cancer 37:780–784

Costa MJ, Weiss SW (1990) Angiomatoid malignant fibrous histiocytoma. A follow-up study of 108 cases with evaluation of possible histologic predictors of outcome. Am J Surg Pathol 14:1126–1132

Curtis RE, Rowlings PA, Deeg HJ et al (1997) Solid cancers after bone marrow transplantation. N Engl J Med 336:897–904

Danietti M, Ferrari A, Frigerio S et al (2009) Cutaneous melanoma on childhood and adolescence shows frequent loss of INK4A and gain of KIT. J Invest Dermatol 129(7):1759–1768

Deyrup AT, Lee VK, Hill CE et al (2006) Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol 30:75–82

Easton DF, Eeles RA (2008) Genome-wide association studies in cancer. Hum Mol Genet 17(R2):R109–R115

Enzinger FM (1979) Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm. Cancer 44:2147–2157

Enzinger FM, Zhang RY (1988) Plexiform fibrohistiocytic tumor presenting in children and young adults. An analysis of 65 cases. Am J Surg Pathol 12:818–826

Euvrard S, Kanitakis J, Claudy A (2003) Skin cancers after organ transplantation. N Engl J Med 348:1681–1691

Fahrtash F, McCahon E, Arbuckle S (2010) Successful treatment of kaposiform hemangioendothelioma and tufted angioma with vincristine. J Pediatr Hematol Oncol 32:506–510

Fanburg-Smith JC, Miettinen M (1999) Angiomatoid "malignant" fibrous histiocytoma: a clinicopathologic study of 158 cases and further exploration of the myoid phenotype. Hum Pathol 30:1336–1343

Fears TR, Bird CC, Guerry D et al (2002) Average midrange ultraviolet radiation flux and time outdoors predict melanoma risk. Cancer Res 62(14):3992–3996

Ferrari A, Casanova M, Meazza C et al (2001) Vascular tumors in pediatric age. The experience of the Italian and German Cooperative Group. Ital J Pediatr 27:774–778

Ferrari A, Casanova M, Bisogno G et al (2002) Malignant vascular tumors in children and adolescents: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. Med Pediatr Oncol 39:109–114

Ferrari A, Bono A, Baldi M, Collini P, Casanova M, Pennacchioli E et al (2005) Does melanoma behave better in younger children than in adults? A retrospective study on 33 cases of childhood melanoma from a single institution. Pediatrics 115:649–654

Fiore M, Miceli R, Mussi C et al (2005) Dermatofibrosarcoma Protuberans Treated at a Single Institution: a surgical disease with a high cure rate. J Clin Oncol 23:7669–7675

Flaherty KT, Puzanov I, Kim KB et al (2010) Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809–819

Friedman DL, Whitton J, Leisenring W et al (2010) Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 102:1083–1095

Gerami P, Jewell SS, Morrison LE et al (2009) Fluorescence in situ hybridization (FISH) as an ancillary diagnostic tool in the diagnosis of melanoma. Am J Surg Pathol 33:1146–1156

Gibbs P, Moore A, Robinson W et al (2000) Pediatric melanoma: are recent advances in the management of adult melanoma relevant to the pediatric population. J Pediatr Hematol Oncol 22:428–432

Giblin AV, Clover AJ, Athanassopoulos A, Budny PG (2007) Pyogenic granuloma – the quest for optimum treatment: audit of treatment of 408 cases. J Plast Reconstr Aesthet Surg 60:1030–1035

Gilchrest BA, Eller MS, Geller AC, Yaar M (1999) The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med 340(17):1341–1348

Gill M, Renwick N, Silvers DN, Celebi JT (2004) Lack of BRAF mutations in Spitz nevi. J Invest Dermatol 122:1325–1326

Godfrey JC, Vaughan MC, Williams JV (2003) Successful treatment of bowenoid papulosis in a 9-year-old girl with verti-

cally acquired human immunodeficiency virus. Pediatrics 112:e73–e76
Gooskens SL, Oranje AP, van Adrichem LN et al (2010) Imatinib mesylate for children with dermatofibrosarcoma protuberans (DFSP). Pediatr Blood Cancer 55:369–373
Goto M, Miller RW, Ishikawa Y, Sugano H (1996) Excess of rare cancers in Werner syndrome (adult progeria). Cancer Epidemiol Biomarkers Prev 5:239–246
Haggstrom AN, Drolet BA, Baselga E et al (2006) Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. Pediatrics 118(3):882–887
Hale EK, Stein J, Ben-Porat L et al (2005) Association of melanoma and neurocutaneous melanocytosis with large congenital melanocytic naevi – results from the NYU-LCMN registry. Br J Dermatol 152:512–517
Hamre MR, Chuba P, Bakhshi S et al (2002) Cutaneous melanoma in childhood and adolescence. Pediatr Hematol Oncol 19:309–317
Handfield-Jones SE, Smith NP (1996) Malignant melanoma in childhood. Br J Dermatol 134:607–616
Hayward NK (2003) Genetics of melanoma predisposition. Oncogene 22:3053–3062
Hodi FS, O'Day SJ, McDermott DF et al (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711–723
Horn HM, Tidman MJ (2002) The clinical spectrum of dystrophic epidermolysis bullosa. Br J Dermatol 146:267–274
Isowa N, Hasegawa S, Mino M et al (2002) Mediastinal epithelioid hemangioendothelioma resected by Hemi-Plastron Window technique. Ann Thorac Surg 74:567–569
Jafarian F, McCuaig C, Kokta V, Laberge L, Ben Nejma B (2008) Dermatofibrosarcoma protuberans in childhood and adolescence: report of eight patients. Pediatr Dermatol 25:317–325
Jensen P, Hansen S, Moller B et al (1999) Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 40:177–186
Jha P, Moosavi C, Fanburg-Smith JC (2007) Giant cell fibroblastoma: an update and addition of 86 new cases from the Armed Forces Institute of Pathology, in honor of Dr. Franz M. Enzinger. Ann Diagn Pathol 11:81–88
Karlsson P, Boeryd B, Sander B et al (1998) Increasing incidence of cutaneous malignant melanoma in children and adolescents 12–19 years of age in Sweden 1973–1992. Acta Derm Venereol 78:289–292
Kassi K, Kouame K, Allen W et al (2010) Squamous cell carcinoma secondary to Buruli ulcer: a clinical case report in a young girl. Bacteriol Virusol Parazitol Epidemiol 55:25–28
Kaste SC, Pappo AS, Jenkins JJ III, Pratt CB (1996) Malignant melanoma in children: imaging spectrum. Pediatr Radiol 26:800–805
Kehagias DT, Moulopoulos LA, Antoniou A, Psychogios V, Vourtsi A, Vlahos LJ (2000) Hepatic epithelioid hemangioendothelioma: MR imaging findings. Hepatogastroenterology 47:1711–1713
Kelleher MB, Iwatsuki S, Sheahan DG (1989) Epithelioid hemangioendothelioma of liver. Clinicopathological correlation of 10 cases treated by orthotopic liver transplantation. Am J Surg Pathol 13(12):999–1008
Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U (2004) A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res 10:1670–1677
Kleinerman RA, Tucker MA, Tarone RE et al (2005) Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol 23:2272–2279
Kraemer KH, Lee MM, Scotto J (1987) Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol 123:241–250
Kraemer KH, DiGiovanna JJ, Moshell AN, Tarone RE, Peck GL (1988) Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. N Engl J Med 318:1633–1637
Kraemer KH, Levy DD, Parris CN et al (1994) Xeroderma pigmentosum and related disorders: examining the linkage between defective DNA repair and cancer. J Invest Dermatol 103:96S–101S
Kumar P, Ladas GP, Judson I, Nicholson AG (2003) Epithelioid hemangioendothelioma and other vascular mediastinal tumors: a role for alpha-2a interferon? Ann Thorac Surg 76(2):653
Lange JR, Palis BE, Chang DC, Soong SJ, Balch CM (2007) Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. J Clin Oncol 25:1363–1368
Lazovich D, Vogel RI, Berwick M, Weinstock MA, Anderson KE, Warshaw EM (2010) Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. Cancer Epidemiol Biomarkers Prev 19:1557–1568
Léauté-Labrèze C, Dumas de la Roque E, Hubiche T et al (2008) Propranolol for severe hemangiomas of infancy. N Engl J Med 358:2649–2651. doi:24
Leman JA, Evans A, Mooi W, Mackie RM (2005) Outcomes and pathological review of a cohort of children with melanoma. Br J Dermatol 152(6):1321–1323
Lohmann CM, Coit DG, Brady MS, Berwick M, Busam KJ (2002) Sentinel lymph node biopsy in patients with diagnostically controversial spitzoid melanocytic tumors. Am J Surg Pathol 26:47–55
Loria D, Matos E (2001) Risk factors for cutaneous melanoma: a case-control study in Argentina. Int J Dermatol 40(2): 108–114
Luzar B, Calonje E (2010) Cutaneous fibrohistiocytic tumours – an update. Histopathology 56:148–165
Lyburn ID, Torreggiani WC, Harris AC et al (2003) Hepatic epithelioid hemangioendothelioma: sonographic, CT, and MR imaging appearances. AJR 180:1359–1364
Madariaga JR, Marino IR, Karavias DD et al (1995) Long-term results after liver transplantation for primary hepatic epithelioid hemangioendothelioma. Ann Surg Oncol 2(6):483–487
Makkar HS, Frieden IJ (2004) Neurocutaneous melanosis. Semin Cutan Med Surg 23:138–144
Marsciani A, Pericoli R, Alaggio R et al (2010) Massive response of severe infantile hepatic hemangioma to propanolol. Pediatr Blood Cancer 54(1):176
Matsumoto K, Nakanishi H, Seike T, Koizumi Y, Mihara K, Kubo Y (2001) Treatment of pyogenic granuloma with a sclerosing agent. Dermatol Surg 27:521–523
Mazereeuw-Hautier J, Hoeger PH, Benlahrech S et al (2010) Efficacy of propranolol in hepatic infantile hemangiomas with diffuse neonatal hemangiomatosis. J Pediatr 157(2):340–342

McArthur G (2007) Dermatofibrosarcoma protuberans: recent clinical progress. Ann Surg Oncol 14:2876–2886
McKee PH, Fletcher CD (1991) Dermatofibrosarcoma protuberans presenting in infancy and childhood. J Cutan Pathol 18:241–246
Melnik MK, Urdaneta LF, Al-Jurf AS, Foucar E, Jochimsen PR, Soper RT (1986) Malignant melanoma in childhood and adolescence. Am Surg 52:142–147
Mentzel T, Beham A, Calonje E et al (1997) Epithelioid hemangioendothelioma of skin and soft tissues: clinicopathologic and immunohistochemical study of 30 cases. Am J Surg Pathol 21:363
Mentzel T, Beham A, Katenkamp D, Dei Tos AP, Fletcher CD (1998) Fibrosarcomatous ("high-grade") dermatofibrosarcoma protuberans: clinicopathologic and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. Am J Surg Pathol 22:576–587
Milton GW, Shaw HM, Thompson JF, McCarthy WH (1997) Cutaneous melanoma in childhood: incidence and prognosis. Australas J Dermatol 38:44–48
Moehrle M, Breuninger H, Rocken M (2007) A confusing world: what to call histology of three-dimensional tumour margins? J Eur Acad Dermatol Venereol 21:591–595
Mones JM, Ackerman AB (2003) Melanomas in prepubescent children. Review comprehensively, critique historically, criteria diagnostically, and course biologically. Am J Dermatopathol 25:223–238
Mones JM, Ackerman AB (2004) "Atypical" Spitz's nevus, "malignant" Spitz's nevus, and "metastasizing" Spitz's nevus: a critique in historical perspective of three concepts flawed fatally. Am J Dermatopathol 26:310–333
Moosavi C, Jha P, Fanburg-Smith JC (2007) An update on plexiform fibrohistiocytic tumor and addition of 66 new cases from the Armed Forces Institute of Pathology, in honor of Franz M. Enzinger, MD. Ann Diagn Pathol 11:313–319
Morton DL, Thompson JF, Cochran AJ et al (2006) Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 355:1307–1317
Muftuoglu M, Oshima J, von Kobbe C, Cheng WH, Leistritz DF, Bohr VA (2008) The clinical characteristics of Werner syndrome: molecular and biochemical diagnosis. Hum Genet 124:369–377
Navid F, Furman WL, Fleming M et al (2005) The feasibility of adjuvant interferon alpha-2b in children with high-risk melanoma. Cancer 103:780–787
Pappo AS, Rao BN, Cain A, Bodner S, Pratt CB (1997) Dermatofibrosarcoma protuberans: the pediatric experience at St. Jude Children's Research Hospital. Pediatr Hematol Oncol 14:563–568
Paradela S, Fonseca E, Pita-Fernandez S et al (2010) Prognostic factors for melanoma in children and adolescents: a clinicopathologic, single-center study of 137 patients. Cancer 116:4334–4344
Pastore G, De Salvo GL, Bisogno G et al (2009) Evaluating the access to pediatric cancer care centres of children and adolescents with rare tumors in Italy: the TREP project. Pediatr Blood Cancer 53:152–155
Pearce MS, Parker L, Cotterill SJ et al (2003) Skin cancer in children and young adults: 28 years' experience from the Northern Region Young Person's Malignant Disease Registry, UK. Melanoma Res 13(4):421–426
Penel N, Bui B, Bay JO et al (2008) Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX study. J Clin Oncol 26:5269–5274
Penel N, Marreaud S, Robin YM, Hohenberger P (2010) Angiosarcoma: state of the art and perspectives. Crit Rev Oncol Hematol. Nov. 3 (Epub ahead of print)
Penn I (1994) De novo malignancy in pediatric organ transplant recipients. J Pediatr Surg 29:221–228
Price VE, Fletcher JA, Zielenska M et al (2005) Imatinib mesylate: an attractive alternative in young children with large, surgically challenging dermatofibrosarcoma protuberans. Pediatr Blood Cancer 44:511–515
Pryor SG, Lewis JE, Weaver AL, Orvidas LJ (2005) Pediatric dermoid cysts of the head and neck. Otolaryngol Head Neck Surg 132:938–942
Rao BN, Hayes FA, Pratt CB et al (1990) Malignant melanoma in children: its management and prognosis. J Pediatr Surg 25:198–203
Ribeiro RC, Rill D, Roberson PK et al (1993) Continuous infusion of interleukin-2 in children with refractory malignancies. Cancer 72:623–628
Ries L SM, Gurney J, Tamra T, Young J, Bunin G (1999) Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. National Cancer Institute SEER Program NIH Pub 99-4649, Bethesda
Rizzo C, Brightman L, Chapas A et al (2009) Outcomes of childhood hemangiomas treated with the pulsed dye laser with dynamic cooling: a retrospective chart analysis. Dermatol Surg 35:1947–1954
Roaten JB, Partrick DA, Bensard D et al (2005) Survival in sentinel lymph node-positive pediatric melanoma. J Pediatr Surg 40(6):988–992
Roudier-Pujol C, Enjolras O, Lacronique J et al (1994) Multifocal epithelioid hemangioendothelioma with partial remission after interferon alfa-2a treatment. Ann Dermatol Venereol 121(12):898–904
Rubin BP, Schuetze SM, Eary JF et al (2002) Molecular targeting of platelet-derived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. J Clin Oncol 20:3586–3591
Rutkowski P, Van Glabbeke M, Rankin CJ et al (2010) Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol 28:1772–1779
Saenz NC, Saenz-Badillos J, Busam K et al (1999) Childhood melanoma survival. Cancer 85:750–754
Sahin G, Palanduz A, Aydogan G et al (2010) Classic Kaposi sarcoma in 3 unrelated Turkish children born to consanguineous kindreds. Pediatrics 125:e704–e708
Salomao DR, Nascimento AG (1997) Plexiform fibrohistiocytic tumor with systemic metastases: a case report. Am J Surg Pathol 21:469–476
Sander B, Karlsson P, Rosdahl I et al (1999) Cutaneous malignant melanoma in Swedish children and teenagers 1973-1992: a clinico-pathological study of 130 cases. Int J Cancer 80:646–651
Schmid-Wendtner MH, Berking C, Baumert J et al (2002) Cutaneous melanoma in childhood and adolescence: an analysis of 36 patients. J Am Acad Dermatol 46:874–879
Scoazec JY, Lamy P, Degott C et al (1988) Epithelioid hemangioendothelioma of the liver. Diagnostic features and role of liver transplantation. Gastroenterology 94(6):1447–1453

Shah NC, Gerstle JT, Stuart M, Winter C, Pappo A (2006) Use of sentinel lymph node biopsy and high-dose interferon in pediatric patients with high-risk melanoma: the Hospital for Sick Children experience. J Pediatr Hematol Oncol 28: 496–500

Sondak VK, Cimmino VM, Lowe LM, Dubay DA, Johnson TM (1999) Dermatofibrosarcoma protuberans: what is the best surgical approach? Surg Oncol 8:183–189

Spatz A, Ruiter D, Hardmeier T et al (1996) Melanoma in childhood: an EORTC-MCG multicenter study on the clinicopathological aspects. Int J Cancer 4:317–324

Spitz S (1948) Melanomas of childhood. Am J Pathol 24: 591–609

Strouse JJ, Fears TR, Tucker MA, Wayne AS (2005) Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol 23:4735–4741

Su LD, Fullen DR, Sondak VK, Johnson TM, Lowe L (2003) Sentinel lymph node biopsy for patients with problematic spitzoid melanocytic lesions: a report on 18 patients. Cancer 97:499–507

Sybert V (1991) Six children with malignant melanoma. J Am Acad Dermatol 24:666–667

Taher A, Pushpanathan C (2007) Plexiform fibrohistiocytic tumor: a brief review. Arch Pathol Lab Med 131: 1135–1138

Tate PS, Ronan SG, Feucht KA et al (1993) Melanoma in childhood and adolescence: clinical and pathological features of 48 cases. J Pediatr Surg 28:217–222

Tay YK, Weston WL, Morelli JG (1997) Treatment of pyogenic granuloma in children with the flashlamp-pumped pulsed dye laser. Pediatrics 99:368–370

Terrier-Lacombe MJ, Guillou L, Maire G et al (2003) Dermatofibrosarcoma protuberans, giant cell fibroblastoma, and hybrid lesions in children: clinicopathologic comparative analysis of 28 cases with molecular data – a study from the French Federation of Cancer Centers Sarcoma Group. Am J Surg Pathol 27:27–39

Terui K, Nakatani Y, Kambe M, Fukunaga M, Hishiki T, Saito T, Sato Y, Takenouchi A, Saito E, Ono S, Yoshida H (2010) Kaposiform hemangioendothelioma of the choledochus. J Pediatr Surg 45:1887–1889

Thway K (2008) Angiomatoid fibrous histiocytoma: a review with recent genetic findings. Arch Pathol Lab Med 132:273–277

Toyoda H, Ido M, Nakanishi K et al (2010) Multiple cutaneous squamous cell carcinomas in a patient with interferon gamma receptor 2 (IFN gamma R2) deficiency. J Med Genet 47:631–634

Tulpule A, Yung RC, Wernz J, Espina BM, Myers A, Scadden DT, Cabriales S, Ilaw M, Boswell W, Gill PS (1998) Phase II trial of liposomal daunorubicin in the treatment of AIDS-related pulmonary Kaposi's sarcoma. J Clin Oncol 16:3369–3374

Uribe P, Wistuba II, Solar A et al (2005) Comparative analysis of loss of heterozygosity and microsatellite instability in adult and pediatric melanoma. Am J Dermatopathol 27:279–285

Wechsler J, Bastuji-Garin S, Spatz A et al (2002) Reliability of the histopathologic diagnosis of malignant melanoma in childhood. Arch Dermatol 138(5):625–628

Weiss SW, Enzinger FM (1982) Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer 50:970–981

Whiteman D, Valery P, McWhirter W, Green A (1995) Incidence of cutaneous childhood melanoma in Queensland, Australia. Int J Cancer 63:765–768

Whiteman DC, Milligan A, Welch J et al (1997) Germline CDKN2A mutations in childhood melanoma. J Natl Cancer Inst 89:1460

Wilson MW, Hoehn ME, Haik BG, Rieman M, Reiss U (2007) Low-dose cyclophosphamide and interferon alfa 2a for the treatment of capillary hemangioma of the orbit. Ophthalmology 114(5):1007–1011

Wollina U, Buslau M, Weyers W (2002) Squamous cell carcinoma in pansclerotic morphea of childhood. Pediatr Dermatol 19:151–154

Youl P, Aitken J, Hayward N et al (2002) Melanoma in adolescents: a case-control study of risk factors in Queensland, Australia. Int J Cancer 98:92–98

Yuksekkaya HA, Arikan C, Yazici A et al (2009) Successful treatment of a child having generalized Kaposi's sarcoma after living donor liver transplantation with conversion to sirolimus. Pediatr Transplant 13:375–378

Ziegler JL, Katongole-Mbidde E (1996) Kaposi's sarcoma in childhood: an analysis of 100 cases from Uganda and relationship to HIV infection. Int J Cancer 65:200–203

Zuckerman R, Maier JP, Guiney WB Jr et al (2001) Pediatric melanoma: confirming the diagnosis with sentinel node biopsy. Ann Plast Surg 46:394–399

Part XI

Rare Mesenchymal Tumors

Rare Mesenchymal Tumors

44

Andrea Ferrari, Rita Alaggio, and Stefano Ferrari

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44.1 Non-rhabdomyosarcoma Soft Tissue Sarcomas

Andrea Ferrari and Rita Alaggio

While benign neoplasms of soft tissues (i.e., lipoma, fibroma, leiomyoma, hemangioma) are relatively frequent and outnumber by 100 times malignant cases (incidence of about 300 new cases per 100,000), soft tissue sarcomas are rare diseases. They account for <1% of all malignant tumors and 2% of all cancer-related deaths. Data from the Survival Epidemiology and End Result (SEER) registry indicated an overall incidence of 5.9/100,000 persons/year. The incidence rates increased with age, rising from 0.9/100,000 in children younger than age 10 years to 18.2 for individuals older than age 70 (Ferrari et al. 2011).

However, though their absolute number is lower than in adult age, in childhood and adolescence, soft part sarcomas encounter for about 8% of all malignancies and as a whole group represents the fifth most frequent childhood cancer. More than half of pediatric soft tissue sarcomas are represented by rhabdomyosarcoma, that is one of the most typical tumors of childhood. The remaining entities are usually grouped under the definition of "non-rhabdomyosarcoma soft tissue sarcomas" (NRSTS), a term that describes a heterogeneous group of mesenchymal extraskeletal malignant tumors: Some of them are peculiar of infants and small children, but most of the entities included in this group are really tumors more common in adults than in children (Fig. 44.1). The term "NRSTS" (currently in widespread use) reflects the fact that these tumors have been historically managed according to

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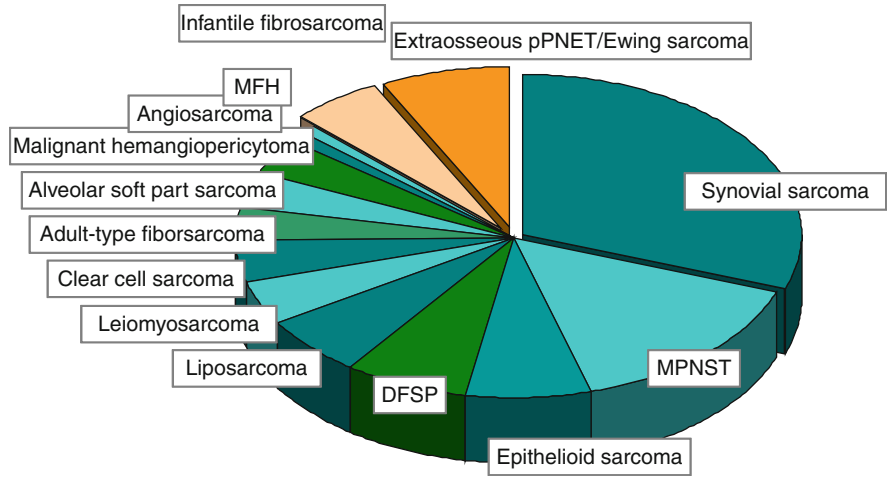

Fig. 44.1 Different non-rhabdomyosarcoma soft tissue sarcoma histotypes in the series from the Istituto Nazionale Tumori in Milan (Ferrari et al. 2005a). In *blue-green colors*, the "adult-type" subtypes. *pPNET* peripheral primitive neuroectodermal tumors, *MPNST* malignant peripheral nerve sheath tumors, *DFSP* dermatofibrosarcoma protuberans, *MFH* malignant fibrous histiocytoma

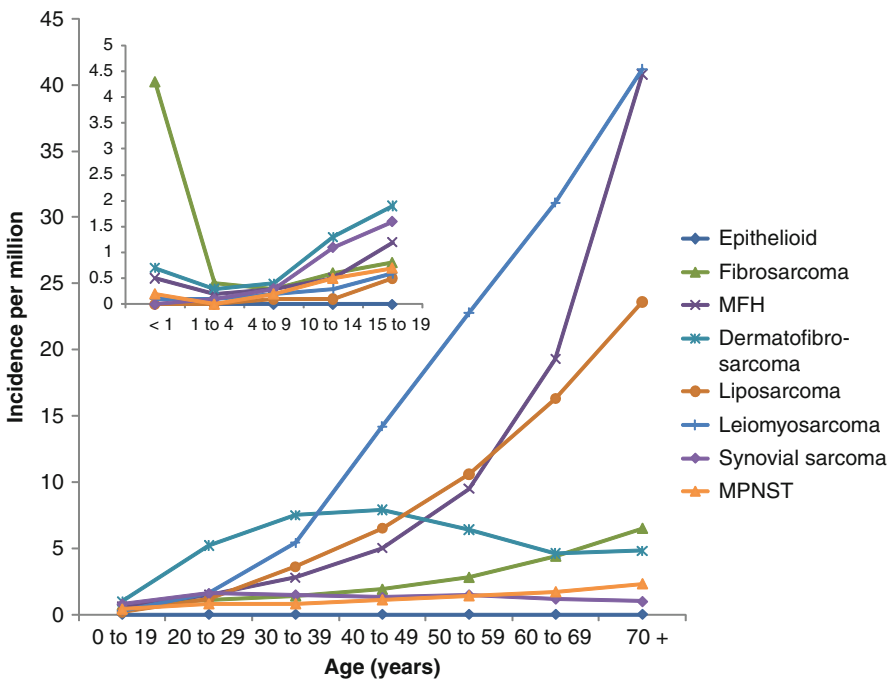

Fig. 44.2 Age-specific incidence of some non-rhabdomyosarcoma soft tissue sarcoma subtypes from the Survival Epidemiology and End Result (SEER) public-access database collected from various geographic areas in the United States (1973–2007) (www.seer.cancer.gov) (Courtesy Dr. Iyad Sultan, King Hussein Cancer Center, Amman, Jordan)

the principles adopted for rhabdomyosarcoma, but, though they share some clinical characteristics, NRSTS must be considered as clearly different entities. Each NRSTS histotype should be considered a very rare tumor in childhood. As examples, Fig. 44.2 shows the age-specific incidence of some subtypes from the SEER: synovial sarcoma, dermatofibrosarcoma protuberans, and malignant peripheral nerve sheath tumors (MPNST).

NRSTS can arise anywhere in the body, and can have a local invasiveness and a tendency to give distant metastases that is correlated to the different degrees of malignancy along histotype and tumor grade. As a general view, borderline and low-grade tumors may be locally aggressive, but unlikely to metastasize: The growth rate may be indolent and sometimes the diagnosis is done after removing a small swelling that has existed for several years. High-grade tumors are more aggressive and can have a strong propensity to metastasize, particularly to the lung. The clinical history may be very different among the different entities included under the NRSTS umbrella: e.g., MPNST are generally axial and aggressiveness disease, characterized by poor prognosis, particularly when associated to neurofibromatosis type 1 (NF1) (Ferrari et al. 2007a; Carli et al. 2005); epithelioid sarcomas present typical

features such as peculiar superficial distal location (i.e., hand, fingers), indolent growth and tendency for lymph node involvement (Casanova et al. 2006); infantile fibrosarcomas is a peculiar subtype that may have initial rapid growth and metastatic spread, but also indolent evolution (and also spontaneous regressions have been described) (Orbach et al. 2010); desmoplastic small round cell tumors (DSRCT) usually present as large abdominal masses generally disseminated at the time of diagnosis, with extensive spread to regional lymph nodes, peritoneal seeding, and distant metastases; the outcome is extremely poor despite intensive multimodality treatment approaches (Kushner et al. 1996; Bisogno et al. 2010).

As a preliminary statement, it could be said that the rarity and the heterogeneity of NRSTS would suggest that children and adolescents with these tumors should be referred to selected experienced institutions with multidisciplinary skills in enrolling patients in clinical trials. Tumors of intermediate malignancy are usually treated with surgery alone. For truly malignant tumors, and for high-grade sarcomas in particular, a multimodal therapy including surgery, radiotherapy, and chemotherapy needs to be considered the best approach. Most of NRSTS are usually considered scarcely chemosensitive tumors, but this is not true for all the histotypes, some of them requiring peculiar tailored approaches. In all the cases, the indication for the different treatment modalities and their intensity should be modulated according to the risk group, with the aim to give more intensive therapies to patients with less favorable prognostic factors, while avoiding overtreatment and side effects (without jeopardizing the outcome) in cases with more favorable clinical features (Ferrari and Casanova 2005).

The overall cure rate for NRSTS patients, in fact, is around 70%, but this data is strictly correlated to the presence of the different prognostic variables. For most NRSTS, and in particular for those entities typical of adult age (adult-type NRSTS), the variables known to have a prognostic role in adults are relevant also in children (Spunt et al. 1999; Ferrari et al. 2005b, 2007b): the disease extension at onset, the degree of the initial surgery, the grade of malignancy, the tumor site (Ferrari et al. 2008), the tumor size (though it should be considered that the risk associated with a given tumor size may not be the same in patients with the same tumor but of different age and body size) (Ferrari et al. 2009). Patient's age is often a prognostic factor (Hayes-Jordan et al. 2000) and for many NRSTS subtypes, treatment results reported in pediatric series are significantly better than those reported in adult cohorts (Sultan et al. 2009; Ferrari et al. 2004).

While in the past, children with NRSTS were often treated according to the guidelines defined for rhabdomyosarcoma, in the recent years, both the North-American Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG) and the European paediatric Soft tissue sarcoma Study Group (EpSSG) developed specific multimodal risk-adapted trials focused on pediatric NRSTS, the COG ARST0332 and the EpSSG NRSTS 2005.

44.1.1 The Pathological Characterization

The histologic classification of soft tissue tumors is based on their morphologic resemblance to one of the constituent mesenchymal tissues in the different developmental stages. Whether these tumors originate from a mesenchymal stem-cell or from a less primitive precursor committed to a differentiative lineage is still unknown. For a large and heterogeneous group of soft tissue tumors, the putative cell of origin remains a mystery.

The current WHO classification for soft tissue tumors (WHO 2002) recognizes three prognostic categories: benign tumors, malignant tumors, and tumors with intermediate prognosis (locally aggressive and rarely metastasizing). The clinical and histologic overlap between these forms make their diagnosis particularly challenging and complex for both clinicians and pathologists. In case of benign or intermediate tumors, it is important to avoid the risk of a mutilating surgery or overtreatment, and in case of sarcomas, the correct categorization allows the adequate treatment. Although the diagnosis is based on morphology, the widespread use of immunohistochemistry with specific lineage markers and the identification of cytogenetic and molecular genetic abnormalities have contributed to a more precise classification and to a better understanding of the mechanisms involved in tumor development, progression, and prognosis.

Genomic and expression profiling studies suggest that sarcomas can be divided into four major genetic groups: (a) sarcomas with specific translocation, (b) sarcomas with specific activating or inactivating mutations, (c) sarcomas with 12q13-15 amplification, and (d) sarcomas with a complex genomic profile (Chibon et al. 2009; Coindre and Chibon 2010). Most of sarcomas

Table 44.1 Clinicopathologic features of rare soft tissue tumors with intermediate prognosis in children

Differentiative lineage	Histotype	Site	Genetic alterations	Associated syndromes or malformations	Histologic key-features
Fibroblastic myofibroblastic	Superficial fibromatoses	Plantar, less frequently palmar	Autosomal dominant	Spine malformations, bifid uvula, geographic tongue, inflammatory bowel disease, and Ehlers–Danlos-like findings	Proliferation of fibroblasts and plump myofibroblasts in bundles
	Desmoid-type fibromatoses	Abdominal, extra-abdominal	Mutations in APC gene in FAP CTNNB1 (exon 3) in sporadic variants	FAP/Gardner syndrome	Uniform spindle cells in fascicle with thin-walled vessels running parallely, scattered mast cells
	Lipofibromatosis	Distal extremities, trunk, head	t (4;6;9)	–	Mature adipose tissue traversed by fascicles of fibroblasts
	Inflammatory myofibroblastic tumor	Lung, mesentery, omentum, retroperitoneum, liver, head, neck	ALK rearrangements with different partner genes	–	Fasciitis-like, fibrohistiocytoma-like, desmoid-like
	Infantile fibrosarcoma	Trunk, distal extremities	(12;15)(p13;q25)	–	Spindle cells with high nuclear/cytoplasm ratio and nuclear hyperchromasia, in fascicles with herringbone pattern
Vascular	Kaposiform hemangioendothelioma	Retroperitoneum, skin, head, and neck	–	Kasaback–Merrit syndrome	Nodules of capillary-sized vessels intermixed with spindle cells, glomeruloid nests of endothelial cells and dilated lymphatic vessels at periphery

FAP familial adenomatous polyposis

typical of childhood fall in the first group, whereas more than 50% of the adult-type sarcomas are encompassed in the last category, together with some sarcomas arising in the context of family cancer syndromes and those arising as second tumors after radiotherapy.

Tables 44.1 and 44.2 summarize the most frequent pediatric sarcomas other than rhabdomyosarcoma in children and adolescents, the chromosomal aberrations and the associated cancer syndromes.

44.1.2 Soft Tissue Tumors with Intermediate Prognosis

Soft part tumors with intermediate prognosis are mostly of fibroblastic-myofibroblastic origin and include some lesions occurring both in children and adults, such as fibromatoses and inflammatory myofibroblastic tumor, and others occurring exclusively in childhood, such as infantile fibrosarcoma. This group includes also tumors of fibrohistiocytic origin (plexiform fibrohistiocytic tumor), vascular origin (kaposiform hemangioendothelioma), or with unknown histogenesis (angiomatoid fibrous histiocytoma). *Plexiform fibrohistiocytic tumor*, *angiomatoid fibrous histiocytoma*, and *kaposiform hemangioendothelioma* are discussed in the chapter on "rare tumors of the skin and subcutaneous tissue."

These lesions of intermediate malignancy may display a worrisome morphology mimicking highly aggressive sarcomas, and clinical features of a poorly circumscribed mass with infiltrative margins may further support this possibility. They represent a therapeutic challenge for oncologists and surgeons, in particular

in case of large unresectable lesions. Historically, surgery had been generally considered the mainstay of treatment for these tumors. However, treatment strategies are currently changing to some degree, from a strategy of aggressive surgery to a multidisciplinary approach that includes also various potentially effective systemic therapies and takes the functional and cosmetic sequelae of treatments into account too.

44.1.2.1 Fibromatoses

The fibromatoses are benign or intermediate locally aggressive fibroblastic-myofibroblastic proliferations and may be sporadic or associated to syndromes or genetic disorders. Classically, they are divided into juvenile and adult-type fibromatoses (Allen 1977).

The great majority of *juvenile fibromatoses* are benign and include different clinicopathologic entities, some solitary and only occasionally multiple, like fibrous hamartoma of infancy, others frequently multicentric, like myofibromatosis. The clinical behavior may differ from spontaneous regression, either in solitary or multicentric variants, to lethal forms with visceral involvement (Chung and Enzinger 1981). Some other fibromatoses are hereditary, such as juvenile hyaline fibromatosis and gingival fibromatosis (Coffin and Boccon-Gibod 2004).

Lipofibromatosis is the only juvenile fibromatosis classified among the intermediate, soft tissue neoplasms, with recurrences or persistent growth observed after surgery in 72% of cases. It is typical of infants, congenital in 25% of cases, more frequent in males, and generally localized in the upper and lower distal extremities. In the past, many cases had been diagnosed as desmoid fibromatosis. The diagnostic key-feature is the presence of adipose tissue traversed by fibrous septa containing fascicles of bland fibroblasts. Risk of recurrence may be associated with congenital onset, male sex, hands and feet location, incomplete surgery, and a high mitotic activity (Fetsch et al. 2000).

The *adult fibromatoses* include the deep-seated *desmoid fibromatosis* (aggressive fibromatosis) and *superficial palmar/plantar fibromatosis*, both representing intermediate, locally recurring soft tissue neoplasms.

Although considered adult fibromatoses, *desmoid tumors* occur both in adults and children, with an incidence of 0.2–0.4/100,000 population/year. It account for up to 60% of fibrous tumors in childhood, where up to 30% occur in the first year of life, with a peak incidence around 4.5 years. A male predominance has been observed in pediatric series.

The pathogenesis of aggressive fibromatosis is most likely multifactorial and genetic predisposition, endocrine factors, and trauma, all seem to play an important part. This neoplasm can be sporadic or arise in the setting of Familial Adenomatous Polyposis (FAP) or the Gardner's variant of the syndrome, often characterized by intra-abdominal mesenteric lesions with aggressive behavior. Syndromic desmoid may be preceded or accompanied by fibrous, plaque-like lesions called Gardner Fibroma.

Histologically, the lesions vary in cellularity and amount of collagen matrix. Uniform spindle cells and subtle collagen bundles are arranged in long fascicles or sheets with thin-walled blood vessels parallel to the fascicles. Immunostains confirm the fibroblastic-myofibroblastic nature of desmoid fibromatoses, showing positive staining for vimentin and variable expressions of muscle-specific actin, desmin, and smooth muscle actin.

Cytogenetic investigation of desmoids in FAP has clarified the key role played by beta-catenin, a transcriptional activator involved in the promotion of mesenchymal cell proliferation. In FAP-related desmoids, germ-line mutations in APC gene inhibit its ability to induce the phosphorylation of beta-catenin necessary for its proteosomal degradation, and it accumulates in the cytoplasm and migrates to the nucleus with a permanent activation of genes involved in cell proliferation. In sporadic desmoids, mutations more frequently involve codons 41 (41A) and 45 (45F and 45P) of beta-catenin gene CTNNB1 resulting in a non-phosphorylated active beta-catenin. The mutated form of beta-catenin shows a positive nuclear immunostaining (Salas et al. 2010). Some studies indicate that increased nuclear expression of beta-catenin, especially if associated to p53 positivity, may be predictive of a high recurrence rate (wild-type beta-catenin tumors seem to have a better relapse-free survival) and may be potentially used as molecular biomarkers of local recurrence (Dômont et al. 2010; Lazar et al. 2008).

In children, desmoid fibromatosis may involve extremities, trunk, head, and neck. They have a strong tendency for local recurrence (ranging from 24% to 77%), but do not metastasize to other organs as truly malignant tumors do. (Overall survival is generally over 90% at 10 years.)

Table 44.2 Clinicopathologic features of rare malignant soft tissue tumors in children

Differentiative lineage	Histotype	Site	Genetic alterations	Associated syndromes or malformations, predisposing factors	Histologic key features
Fibroblastic myofibroblastic	Adult-type fibrosarcoma	Distal extremities, trunk, head, neck, and lung	–	Previous radiotherapy	Spindle cells with tapered nuclei, in herringbone pattern
	Myofibrosarcoma	Head and neck, rarely bone	Nonspecific alterations at 12p11, 12q13-q22, 1p gain	–	Myofibroblastic differentiation (with EM or IHC)
	Low-grade fibromyxoid sarcoma	Superficial, head and neck, lower extremities, and trunk	t(7;16)(q32-34;p11)	–	Biphasic tumor with myxoid/fibrous areas and bland spindle cells in myxoid stroma with prominent arciform vessels
	Sclerosing epithelioid fibrosarcoma	Deep, limb, trunk, shoulder, neck	t(7;16)(q32-34;p11) in mixed tumors with LGFMS areas	–	Carcinoma-like nests, sheets, or cords of epithelioid cells in a fibrous stroma
	Myxofibrosarcoma	Trunk, distal extremities	–	–	Low-grade: scattered spindle /stellate cells with hyperchromatic nuclei in myxoid matrix
					High grade: increase of cellularity and atypia
Smooth muscle	Leiomyosarcoma	Skin, superficial and deep soft tissue, bone, viscera (lung and GI tract)	Extra copies of chr 5, 18, 20, 21, 22 in infantile form, complex structural and numerical cytogenetic alterations in others		Spindle cells with elongated, blunt-ended nuclei in interlacing bundles; variants: inflammatory and myxoid leiomyosarcoma; epithelioid and pleomorphic leiomyosarcoma exceedingly rare
	Smooth muscle tumors with uncertain malignant potential	Multifocal	–	Immunocompromised patients (associated with Epstein–Barr virus infection)	Well-differentiated mitotic activity <18/10HPF
Adipose	Liposarcoma	Lower extremities, mediastinum	Myxoid liposarcoma: t(12;16) (q13;p11), MDM2 mutation in atypical lipomatous tumor	Li–Fraumeni syndrome	More than 90% myxoid LPS (including pleomorphic and spindle cell variants)
					<5% atypical lipomatous tumors
					<2% pleomorphic liposarcoma
Fibrohistiocytic tumors	Undifferentiated high-grade pleomorphic sarcoma			Family history of cancer previous radiotherapy	Spindle cells in fascicles or sheets and storiform pattern focal pleomorphism
Nerve sheath	MPNST		Mutation of NF1 gene in syndromic MPNST	NF1	Classic spindle cells with weavy nuclei, nuclear palisades
			TP53, p16INK4 mutations		Variants: epithelioid, glandular, triton tumor
Vascular tumors	Epithelioid hemangioendothelioma	Deep soft tissue of extremities, viscera	t(1;3)(p36.3;q25) in 2 cases		Epithelioid cells with cytoplasmic vacuoles in a myxoid stroma
	Angiosarcoma	Heart, mediastinum, breast, deep soft tissue	–	–	Malignant blood vessels, nests, sheets of spindle/epithelioid cells

Uncertain differentiation	Epithelioid sarcoma	Finger, hand, wrist, forearm, Lower extremities, trunk, head and neck, genital areas	INI mutation in 50%	–	Classic: nodules of large, eosinophilic cells, central necrosis, morphologic variants: fibroma-like, dermatofibroma-like, angiomatoid, proximal-type: s prominent epithelioid cells with rhabdoid cells
	Clear cell sarcoma of soft parts	Tendons aponeuroses distal extremities	t(12;22)(q13;q12)		Fascicles/nests of pale, elongated epithelioid cells
	Alveolar soft part sarcoma		ASPSCR1–TFE3		Epithelioid cells in nests. PAS-positive cytoplasmic rhomboid crystals
	Desmoplastic small round cell tumor	Abdominal, pelvic cavity, others sites	t (11; 22)(p13; q12),		Solid sheets, nests or cords of small cells in a desmoplastic stroma
	Extrarenal rhabdoid tumor	Somatic soft tissues, abdomen, pelvis, retroperitoneum, liver, heart, and GI tract	Deletion or mutation of hSNF5/SMARCB1/INI1	Syndrome of predisposition to rhabdoid tumor (germ-line mutation/ deletion of INI1 gene)	Epithelioid cells, large nuclei with prominent nucleoli, cytoplasmic juxtanuclear hyaline globules
	Synovial sarcoma	Any site	t(X;18)(p11.2;q11.2)	–	Monophasic fibrous or epithelial biphasic (spindle and epithelioid cells) poorly differentiated

IHC immunohistochemistry, *EM* electron microscopy, *GI tract* gastrointestinal tract, *Inf LMS* inflammatory leiomyosarcoma, *MPNST* malignant peripheral nerve sheath tumors, *NF1* neurofibromatosis type 1, *LGFMS* low-grade fibromyxoid sarcoma

Surgery had been generally considered the mainstay of treatment for these tumors; the goal should be a microscopically complete resection, but the influence of positive margins on local relapse is still debated, hence a mutilating surgery should be avoided. However, treatment strategies are currently changing: On the one hand, it is clear that surgery is not resolutive in many cases, and, moreover, it might be cause of fibromatosis growth and recurrence. On the other hand, various pharmacological treatments have proved to be relatively effective. Therapeutic options may be non-cytotoxic agents, including hormonal treatment (tamoxifene), nonsteroidal anti-inflammatory drugs and interferon-alpha, or cytotoxic agents, in particular the prolonged low-dose chemotherapy such as the weekly low-dose methotrexate plus vinca alkaloid (vinblastine or vinorelbine) combination. Interesting responses have been seen also using target therapy as imatinib (probably via a mechanism of action not involving c-kit and platelet-derived growth factor receptor [PDGFR]) (Heinrich et al. 2006). The response rate to the various systemic regimens is generally around 50% (or less) (Skapek et al. 2007). The goal of systemic therapy in this disease, however, is not only the tumor shrinkage to permit a subsequent resection (as in malignant tumors), but also the induction of growth arrest and tumor stabilization (Meazza et al. 2010).

Desmoid tumors can remain stable for a long time, with or without primary treatment, and this finding has prompted the suggestion that also a "wait-and-see" strategy (clinical-radiological monitoring alone) might be suitable in cases of non-evolving disease. A watchful waiting strategy is currently suggested by many experts: Therapies should be given only in the event of tumor growth (or in case of life-threatening tumors), and first therapeutic option might be a "minimal-morbidity systemic therapy" (being the combination of low-dose methotrexate plus vinblastine/vinorelbine the first choice) rather than a surgical resection (Bonvalot et al. 2008; Fiore et al. 2009).

Due to the potentially long-term cosmetic or functional morbidity in children, radiation therapy may have a role after failure to chemotherapy, in case of progression despite multiple surgeries, or as alternative to mutilating surgery.

The *superficial fibromatoses*, including *palmar and plantar fibromatosis*, usually affect adults over the age of 40 years and are rare in children (very uncommon before the age of 5 years) (Fetsch et al. 2005; Urban et al. 1996) [33–36]. Both these entities have a genetic predisposition. Palmar fibromatosis involves the ulnar aspect of the palm, whereas plantar fibromatosis affects the medial plantar arch. The tumors involve the aponeuroses and their morphology varies according to the stage of development. (Pediatric lesions are more cellular and show fibroblastic nodules and frequent mitoses; as the lesions evolve, they become hypocellular and collagenized.)

Differently from adults, in children, there is a prevalence of plantar fibromatosis with more frequent occurrence in females. Palmar and plantar fibromatoses may coexist in the same patient, may be bilateral, or may be associated with the involvement of the extensor surface of the finger joints (knuckle pads) and keloids. An association between palmar-plantar fibromatosis and fifth finger clinodactyly has been reported in about 13% of cases, as well as isolated cases of spine malformation, bifid uvula, "geographic" tongue, inflammatory bowel disease, and Ehlers–Danlos-like findings.

The recurrence rate is higher in children than in adults (about 80%). Surgery is essentially the only treatment and is recommended when the contracture is significant; however, recurrence after surgery is frequent. A wide or radical fasciectomy or dermofasciectomy is generally reserved for lesions determining functional impairment (Fetsch et al. 2005).

44.1.2.2 Inflammatory Pseudotumors

The umbrella term "inflammatory pseudotumors" includes reactive and neoplastic lesions characterized by a proliferation of fibroblasts and myofibroblasts with a prominent chronic inflammatory infiltrate (Gleason and Hornick 2008).

Inflammatory myofibroblastic tumor (IMT) is a distinctive neoplasm, observed mainly in children and young adults. It was originally described in the lung, but it involves also mesentery, omentum, retroperitoneum, abdominal soft tissues, liver, head, and neck. A palpable mass may be the clinical presentation, sometimes accompanied by an inflammatory syndrome, microcytic hypochromic anemia, thrombocytosis, polyclonal hyperglobulinemia (Coffin et al. 1995, 1998a).

Macroscopically, IMT are multinodular, non-encapsulated lesions, with a firm consistency, and may reach a large size, especially the intra-abdominal forms, that infiltrate the intestinal wall. Histologically,

IMT are composed of myofibroblasts with scattered large, ganglion-like cells and a prominent inflammatory infiltrate containing plasma cells, lymphocytes, and eosinophils. According to the degree of cellularity, inflammatory infiltrate, and prevalence of myxoid or fibrous stroma, IMT may display different patterns varying from fasciitis-like lesions, with prominent inflammatory infiltrate and myxoid stroma, to those highly cellular fibrohistiocytoma-like, or hypocellular, desmoid-like (Coffin et al. 1998b) (Fig. 44.5d). A round cell variant has been recently described (Chen and Lee 2008).

Immunohistochemistry shows reactivity for vimentin and variable staining for smooth muscle actin, muscle-specific actin, and desmin. In IMT, the ALK gene, located on chromosome 2p23, codifying for a tyrosine kinase receptor, rearranges with a variety of gene partners (TPM3, CLTC, RANBP2, and others) (Bridge et al. 2001), resulting in a persistently activated protein and a positive immunostaining for ALK-1 in approximately 50% (Cessna et al. 2002; Cook et al. 2001; Coffin et al. 2001). ALK-1 is more frequently positive in pediatric tumors and abdominal sites.

The recurrence rate varies according to the anatomical site. Extrapulmonary IMT lesions tend to recur more frequently, with a relapse rate of 25%. Distant metastases occur in <5% of cases, mostly in lung and brain. Tumor size and histologic features do not appear to influence the clinical behavior. However, aneuploidy may indicate a more aggressive potential (Hussong et al. 1999). A group of ALK-negative IMT might have a higher risk of metastasis and unfavorable prognosis (Coffin et al. 2007). Recent studies suggest that round cell IMT carry an ALK-RANBP2 fusion gene and behave aggressively (Chen and Lee 2008). Wide resection is the mainstay of treatment; radiotherapy and systemic treatments (corticosteroids, chemotherapy) have been variously used in high-risk situations, but their role remains to be established yet (Alaggio et al. 2010a).

44.1.2.3 Congenital Infantile Fibrosarcoma

Congenital infantile fibrosarcoma (CIFS) is the most common sarcoma under 1 year of age. It occurs in the first 2 years of life, and near 50% of cases are diagnosed at birth (or, occasionally, in utero) (Chung and Enzinger 1976; Coffin et al. 1994).

Histologically, CIFS display a wide morphologic spectrum. These tumors are generally highly cellular neoplasms, composed of spindle cells with hyperchromatic nuclei arranged in sheets, bands, or fascicles (Fig. 44.5c). A prominent hemangiopericytomatous vasculature is frequent. A focal herringbone pattern may simulate an adult fibrosarcoma. Mitoses are frequent. Immunostains are not specific and are important to exclude other spindle cell sarcomas: Smooth muscle actin, muscle-specific actin, and desmin are variously expressed. CIFS is characterized by the recurrent translocation t(12;15)(p13;q25) with the transcript ETV6-NTRK3, that is shared by cellular mesoblastic nephroma (Knezevich et al. 1998; Bourgeois et al. 2000). In addition, CIFS may have other cytogenetic abnormalities, including trisomy 11; random gains of chromosomes 8,11,17, and 20; and deletion of long arm of chromosome 17 (Bernstein et al. 1994; Dal Cin et al. 1991; Mandahl et al. 1989).

CIFS is generally located in deep soft tissues of distal extremities (and less frequently trunk). Tumors usually have rapid growth and huge size, while distant metastases are rare. However, the prognosis is favorable in the majority of cases, with survival rates between 80% and 100%. Surgery is the mainstay of treatment (Fig. 44.3), but chemotherapy is effective, also utilizing mild alkylating/anthracyclines-free regimens: The VA regimen (vincristine and actinomycin) is the chemotherapy of choice, and more intensive regimen should be considered only in the event of no response to VA chemotherapy (Orbach et al. 2010). Due to the young age of patients, radiotherapy must not be seen as an option.

The widespread use of molecular characterization has allowed the identification of a group of lesions previously classified as CIFS because of their occurrence in infants and their morphologic overlap with primitive forms of CIFS. These tumors, now identified as Primitive Myxoid Mesenchymal Tumor of Infancy (PMMTI), are characterized by a diffuse growth of primitive spindle, polygonal, and round cells embedded in a myxoid stroma with a characteristic prominent vascular network. The few cases studied by RT-PCR lack the ETV6-NTRK3 transcript. PMMTI may have an aggressive behavior: In the published cases, two out of five newborns with available follow-up died of disease and two experienced either distant metastases or local aggressive growth, not responding to chemotherapy. Surgery is the elective treatment, PMMTI being poorly responsive to chemotherapy (Alaggio et al. 2006).

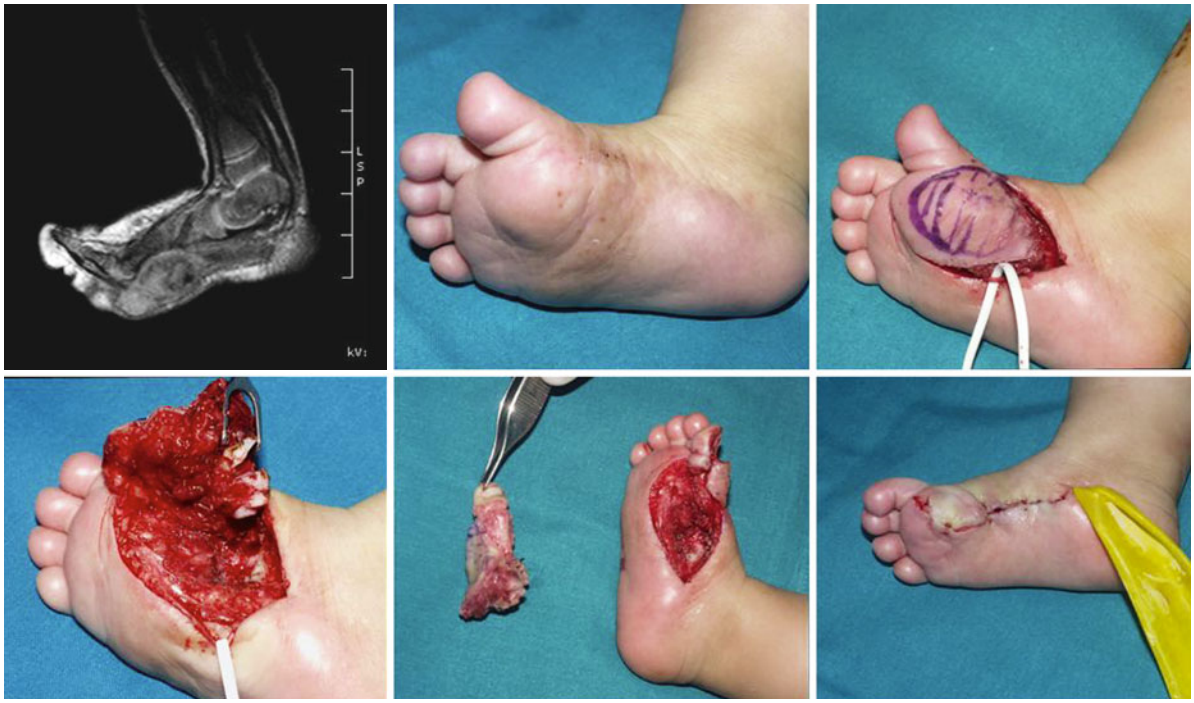

Fig. 44.3 Congenital infantile fibrosarcoma of the right foot. Wide surgical resection with amputation of the first finger (Courtesy Dr. Alessandro Gronchi, Melanoma Sarcoma Surgical Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy)

44.1.3 Malignant Soft Tissue Tumors

The large part of NRSTS represent the so-called adult-type sarcomas, tumor entities typically occurring in adults and elders and only occasionally in children. Most of them show an identifiable differentiative lineage and include adult fibrosarcomas, liposarcoma, leiomyosarcomas, and MPNST. A common denominator in this group of tumors (with the exclusion of MPNST) is the prognostic role of tumor grade. The two most widely used grading systems are the NCI (United States National Cancer Institute) system, which has been adapted for pediatric sarcomas in the POG (Pediatric Oncology Group) system (Parham et al. 1995) and the FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system (Coindre et al. 1996; Guillou et al. 1997a). All have proven to be highly predictive of prognosis in this group of sarcomas. FNCLCC system identifies three grades, grade 1 the lowest, 2 intermediate, and 3 the highest, resulting from the addition of different scores given to tumor resemblance to its normal counterpart, mitotic activity, and necrosis. POG system takes into account the peculiarity of pediatric sarcomas which are considered by definition grade 1 or 3 according to histotype, whereas only adult-type sarcomas are graded according to mitotic rate and necrosis. Currently both FNCLCC and POG systems are being used in pediatric sarcomas.

Synovial sarcoma, alveolar soft part sarcoma, clear cell sarcoma of soft parts, epithelioid sarcoma, desmoplastic small round cell tumor, and rhabdoid tumor are characterized by the absence of a lineage differentiation or an identifiable normal cellular counterpart. With the partial exception of synovial sarcoma, their behavior is not influenced by tumor grade. All these tumors, but rhabdoid tumor, arise in young adults and adolescents and are less frequent in elders and children.

Dermatofibrosarcoma protuberans, *angiosarcoma*, and *epithelioid hemangioendothelioma* (this defined by the WHO as a malignant vascular tumor because of its metastatic risk) are discussed in the chapter on "rare tumors of the skin and subcutaneous tissue."

44.1.3.1 Treatment Strategy

The treatment management of adult-type NRSTS is complex and necessarily multidisciplinary (Table 44.3).

Table 44.3 A general view: practical diagnostic and therapeutic guidelines for pediatric soft tissue sarcomas

Physical examination	Soft tissue mass Signs of neurofibromatosis type 1, i.e., multiple café-au-lait spots, axillary or inguinal freckling, neurofibromas, Lisch nodules (iris hamartomas), plus learning disabilities
Laboratory assessment	No specific tumor markers available
Radiological assessment	
–First assessment	Ultrasonogram
–Local staging	Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site is mandatory for local extension assessment before any treatment. MRI is usually considered superior in defining soft tissue extension
–Diagnostic work	Chest CT scan to identify lung metastases, in high-grade sarcomas Abdominal ultrasound, ultrasound of regional lymph nodes *Technetium bone scan and positron emission tomography* (*PET*) *are not considered a standard staging investigation* (*eventually in high-grade tumors*)
Pathological assessment	In the case of a large and deep soft tissue mass, biopsy should be always the initial surgical procedure, in order to avoid inadequate surgery. The initial biopsy (incisional biopsy or core needle biopsy) has the aim to define the diagnosis, but also should provide enough material for immunochemistry, cytogenetics, biological studies, and central pathology review for patients to be included in clinical trials Histological subtype Tumor grade
Staging systems for risk-adapted treatment strategy	*TNM classification* based on local invasiveness, *T1* and *T2*, and tumor size, *A* or *B*, i.e., less or more than 5 cm; *N0/N1* and *M0/M1*: absence or presence of nodal and distant involvement *Intergroup Rhabdomyosarcoma Study* (*IRS*) *postsurgical grouping systemgroup I* – completely excised tumors with negative microscopic margins; *group II* – grossly resected tumors with microscopic residual disease and/or regional lymph nodal spread; *group III* – gross residual disease after incomplete resection or biopsy; group IV – metastases at onset
General treatment guidelines	Need for multidisciplinary approach
–Surgery	Keystone of treatment Goal: complete and non-mutilating resection Importance of the referral to specialist centers
–Radiotherapy	Well-defined role in local control, after incomplete resection or after wide excision in case of high-grade and large tumor *Indication stricter in younger children due to the higher risk of severe late effects*
–Chemotherapy	Doxorubicin-/ifosfamide-based chemotherapy in unresected tumors Adjuvant chemotherapy in high-grade and large sized sarcomas (especially in synovial sarcomas)

These tumor types are usually considered scarcely sensitive to chemotherapy (tumor response in the range of 40% or less), and surgery thus remains the unquestionable keystone of treatment. Radiotherapy plays a well-defined role in local control, after incomplete resection and, according to adult experiences, also after wide excision, especially in case of large tumors. However, the indication for radiotherapy are usually stricter in children, given the higher risk of severe late effects (i.e., the risk of retardation or arrest of irradiated bone growth, the risk of functional impairment, and that of second post-irradiation tumor). Aggressiveness and intensity of surgery and radiotherapy should be discussed and customized for each patient (taking into account the anatomical site, tumor size, patient's age, response to initial chemotherapy), considering the need to maximize the chances of local control, but also containing the sequelae and preserve function (Ferrari and Casanova 2005).

The role of chemotherapy as part of the multidisciplinary approach in adult-type NRSTS remains uncertain. Chemotherapy is usually given in front-line treatment in patients with advanced unresectable disease (and also in all cases where the surgeon is unsure of being able to achieve a complete resection at the first attempt). Neo-adjuvant chemotherapy may have a role in converting these cases into conservative complete resections, but it may play an important role also in treating any micrometastases promptly (Ferrari et al. 2005b; Spunt et al. 2002; Pappo et al. 2005).

Recently, various international research groups pooled their series on unresected NRSTS in a joint

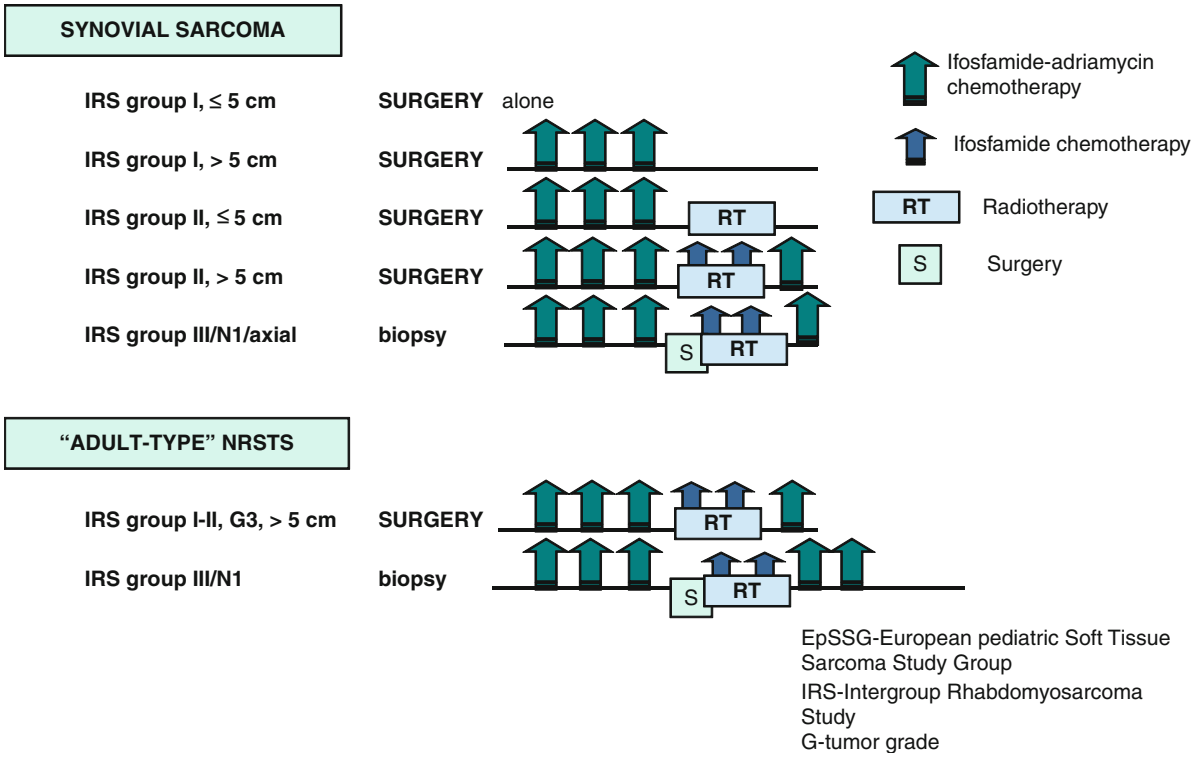

Fig. 44.4 Risk-adapted treatment strategy in the European pediatric Soft tissue sarcoma Study Group (EpSSG) NRSTS 2005 protocol for synovial sarcoma and adult-type NRSTS patients

study comprising 304 patients (Ferrari et al. 2011). Response rate to chemotherapy was 41% in terms of major responses, but also minor responses were seen (16%). Overall survival at 10 years was roughly 50%, and was associated with patient's age, histological subtype, and tumor site and size. MPNST was the tumor type with the worst rate of response to chemotherapy and the worst outcome. Patients who respond to chemotherapy have better chances of survival, as well as those who had a complete delayed surgical resection and those treated with radiotherapy, suggesting that intensive multimodal treatment should be recommended in these patients.

A major debate concern whether or not to provide adjuvant chemotherapy for adult-type soft tissue sarcomas, in order to prevent distant recurrences after initial surgery. Patients outcome after initial resection is good (survival rate up to 90%) in patients with small and low-grade tumor, but the prognosis for patients with high-grade and large invasive tumors is often unsatisfactory, when treated with local therapy alone, even after initial microscopically complete resection, because of a high risk of developing lung metastases (Ferrari et al. 2005a). Pediatric retrospective studies confirmed that in group I-II patients, the combination of two variables – high tumor grade plus large tumor size – gives rise to a very high risk of metastases (metastases-free survival around 30–40%), irrespective of the results of initial surgery, with better survival in those patients who received adjuvant chemotherapy, as compared to those who have not been given (Ferrari et al. 2005b).

This would suggest, in principle, the use of systemic chemotherapy to try to improve survival in those selected patients with high tumor grade and large tumor size (Ferrari 2008) (Fig. 44.4). The only randomized trial on adjuvant chemotherapy in pediatric age (conducted by the Pediatric Oncology Group POG between 1986 and 1992) failed to assess the benefits of adjuvant chemotherapy because the majority of patients refused randomization, showing how difficult it is to conduct prospective randomized studies in pediatric patients with such rare tumors, for which no standard therapy has been established (Pratt et al. 1999).

In adult oncology, the discussion on the role of adjuvant chemotherapy in soft tissue sarcomas has always been a point of controversy (Bramwell 2001): On the one hand, we know that most randomized trials performed by international collaborative groups showed no statistically significant benefit for patients given adjuvant chemotherapy (Santoro et al. 1995; Sarcoma Meta-analysis Collaboration 1997); on the other hand, it is emerging that some of these negative results need to be reconsidered since these trials did not use the combinations of drugs currently recognized as the most effective in soft tissue sarcomas (ifosfamide, in particular, was not included in most of these studies), nor had they selected patients most likely to respond to chemotherapy (tumors of diverse histology, grade, and size were grouped together). When these criteria were considered (targeting a selected group of high-risk patients and delivering a regimen of full-dose ifosfamide plus anthracyclines), a more significant beneficial impact emerged: The Italian Sarcoma Group (ISG) was closed in advance (after the enrollment of 104 patients) because an interim analysis showed a clear improvement in the survival of patients receiving adjuvant chemotherapy by comparison with those given local therapy alone (Frustaci et al. 2001).

44.1.3.2 The Fibrosarcoma Family

Until the 1960s, the diagnosis of fibrosarcoma was very common. The identification of specific sarcoma subtypes and the contribution of immunohistochemical and cytogenetic methods to define a more precise classification of spindle cell sarcomas determined a progressive disappearance of fibrosarcomas that became a rarity. In the last decade, the comprehension of the phenotypic plasticity of fibroblasts and the characterization of myofibroblasts have disclosed different subtypes of fibrosarcoma according to the predominance of fibroblasts or myofibroblasts, stromal patterns, recurrent chromosomal aberrations, and variable expression of immunohistochemical markers of myofibroblastic differentiation (fibronectin, desmin, a-SM actin).

Classic fibrosarcoma probably accounts for <1% of adult sarcomas and is most common between the second and sixth decade with equal sex distribution. It is extremely rare in children and may infrequently occur in adolescents, occasionally in association with a previous radiotherapy. The most common site is the distal parts of the extremities, but other uncommon localizations have been reported. Histologically, fibrosarcoma is characterized by spindle cells with tapered nuclei, small nucleoli, and scanty cytoplasm arranged in a typical herringbone pattern. Tumors with prominent myofibroblasts are classified as *myofibrosarcomas* (Fisher 2004; Montgomery et al. 2001).

Myofibrosarcomas are a controversial entity displaying a range of appearances from low-grade lesions, now recognized as an entity in the current WHO classification of soft tissue tumors, to high-grade forms resembling *storiform-pleomorphic malignant fibrous histiocytoma* included in the group of malignant high-grade pleomorphic sarcomas.

Less than 10% of *low-grade myofibrosarcomas* occur in children and privilege the deep soft tissues of head and neck (and rarely bone) (Smith et al. 1995; Keller et al. 2004). There is a slight male predominance with tumor size ranging from 1.5 to 17 cm. Tumors generally have an indolent clinical course, characterized by relapses in about 33% of cases and metastases, even after a long time, in 3–10% of cases, generally involving the lungs.

Low-grade fibromyxoid sarcoma (*LGFMS*) is a slow-growing mass, deeply located in soft tissues of lower extremities and trunk and occasionally head, neck, or spine (Evans 1987). In children, it is generally superficial and involves more frequently the head and neck (Billings et al. 2005). Histologically, the tumors display a typical biphasic pattern, with an abrupt or gradual transition from myxoid to fibrous, heavily collagenized areas. Spindle cells with bland nuclei, lacking pleomorphism are embedded in an abundant myxoid stroma, containing prominent vessels in an arcade-like configuration. Scattered giant rosettes, with a central zone of eosinophilic collagen surrounded by spindled and epithelioid cells, characterize the variant of LGFMS called hyalinizing spindle cell tumor with giant rosettes (Lane et al. 1997; Folpe et al. 2000a). LGFMS shows specific recurrent translocations involving the FUS gene: FUS-CREB3L2 transcript resulting from translocation t(7;16)(q32-34;p11), and the less frequent FUS-CREB3L1 from t(11;16)(p11;p11) (Mertens et al. 2005; Guillou et al. 2007). If completely excised, LGFMS has a relapse rate of 10%. Metastases may occur even many years after the initial diagnosis in 5–26% of cases. Superficial lesions have a more favorable prognosis (Folpe et al. 2000b).

Sclerosing epithelioid fibrosarcoma is probably a combination of different entities, some falling within

the spectrum of LGFMS and others not jet clearly defined (Meis-Kindblom et al. 1995). It is typical of adults and only 10% of patients are younger than 20 years. The tumors, often large in size, are deeply located in muscles in the lower limb, trunk, shoulder, and neck. Histologically, the tumors show epithelioid or fusiform cells with bland nuclei and clear cytoplasms arranged in carcinoma-like nests, sheets, or cords and embedded in a fibrous stroma or sclerotic matrix (Fig. 44.6d). Cytogenetic features of sclerosing epithelioid fibrosarcoma have been poorly investigated. Recently FUS-CREB3L2 transcripts typical of low-grade fibromyxoid sarcoma have been found in lesions with mixed features of sclerosing epithelioid fibrosarcomas and LGFMS (Guillou et al. 2007).

Due to the heterogeneity of tumors included in the category of sclerosing epithelioid fibrosarcoma, its prognosis remains controversial. An aggressive behavior with persistent disease or local recurrence has been reported in more than 50% of patients, with a metastatic rate between 43% and 86%, and a mortality rate between 25% and 57% (Antonescu et al. 2001).

Myxofibrosarcoma, previously considered a myxoid variant of malignant fibrous histiocytomas, has been included in the group of myofibroblastic lesions in the 2002 WHO classification. It is the commonest soft tissue sarcoma in limbs of older adults, whereas it is very rare under 20 years, with only few cases reported in children, mostly occurring in unusual sites (Denschlag et al. 2005). These tumors show a wide morphologic spectrum and include low- and high-grade forms, often coexisting. Scattered spindle or stellate tumor cells with atypical hyperchromatic nuclei embedded in an abundant myxoid matrix are found in low-grade tumors. Cellularity and atypias progressively increase in intermediate- and high-grade variants with evidence of sheets of pleomorphic cells and necrosis. The treatment is surgical resection, and myxofibrosarcoma can recur and metastasize.

Leiomyosarcoma

Smooth muscle tumors are rare in children and adolescents and include hamartomas, benign tumors (such as angioleiomyoma, leiomyoma, and leiomyomatosis), leiomyosarcoma, and smooth muscle tumors of uncertain malignant potential in immunocompromised individuals.

Leiomyosarcomas account for <4% of childhood soft tissue sarcomas; are more frequent in males; and involve skin, superficial and deep soft tissue, bone, and viscera, such as the lung and GI tract. The mean age at diagnosis is 8–11 years and may arise as a second malignancy in patients treated with radiotherapy. Their prognosis is better than that in adults with a survival rate bigger than 70%. Late metastases in unusual sites may be seen (De Saint Aubain Somerhausen and Fletcher 1999; Ferrari et al. 2001). Macroscopically, leiomyosarcomas are large, not encapsulated nodular masses ranging from 1 to 13 cm, with frequent foci of hemorrhage and necrosis. Histologically they are characterized by spindle cells with elongated, blunt-ended nuclei arranged in interlacing bundles. Morphologic variants include: *inflammatory leiomyosarcoma*, showing a prominent mixed inflammatory infiltrate, and *myxoid leiomyosarcoma*, a low-grade variant only rarely metastasizing, with more than 50% of tumor composed of myxoid stroma. *Pleomorphic* and *epithelioid leiomyosarcoma* are very rare in children. Immunohistochemistry shows reactivity for smooth muscle actin, muscle-specific actin, desmin, and h-caldesmon.

Smooth muscle tumors with uncertain malignant potential are less aggressive tumors, mostly occurring in immunocompromised patients. They are generally visceral, often multifocal. Epstein–Barr virus infection is involved in their pathogenesis. Compared to sporadic leiomyosarcoma, the tumors are well-differentiated, with minor cytologic atypia and mitotic activity ranging from 0 to 18 mitoses per 10 high power field (Mueller et al. 1992; Belarezo and Joshi 2002; Deyrup et al. 2006).

Liposarcoma

Liposarcoma is the most common malignant soft tissue tumor in adults. In children, the neoplasms of adipose tissue are relatively infrequent, and liposarcomas account for <3% of all pediatric sarcomas (Shmookler and Enzinger 1983; La Quaglia et al. 1993). While the anatomic distribution is similar in children and adults, the lower extremities, especially the thigh, being the most frequent site of involvement, the histotypes differ substantially. In adults, the *atypical lipomatous neoplasms* (*well-differentiated liposarcomas*) and their high-grade counterpart (*dedifferentiated liposarcoma*) account for approximately 60% of cases, the myxoid and round cell liposarcomas comprise about 35% of cases, and the *pleomorphic liposarcoma* the remaining 5%. In children, the conventional myxoid liposarcoma

is the most frequent histotype, including around 90% of cases (Ferrari et al. 1999; Alaggio et al. 2009). Atypical lipomatous tumors and pleomorphic liposarcoma are very rare, representing <5% and <2% of cases respectively.

Myxoid liposarcomas are characterized by a plexiform vascular pattern; abundant myxoid matrix; and uniform, bland, round cells with lipoblastic differentiation. Some tumors may display round cell areas, even if histologic progression to conventional round cell liposarcomas is very rare in this age group. As in older patients, the great majority of conventional myxoid liposarcomas show evidence of FUS-CHOP gene fusions, reflecting the presence of the t(12;16)(q13;p11). EWSR1-CHOP gene fusions is very rare, and its exact incidence in pediatric myxoid liposarcomas is unknown. Myxoid liposarcomas have a generally indolent clinical course. Round cell component does not necessarily appear to connote a worse prognosis in children; however, myxoid liposarcomas showing a round cell component bigger than 5% should be regarded as high-grade sarcomas in any age group, based on historical data.

Aggressive local growth and death have been reported in children affected by peculiar morphologic variant of myxoid liposarcoma displaying mixed features of conventional myxoid liposarcoma and pleomorphic liposarcoma. Whether it represents a different subtype of liposarcoma, typical of young patients, is still unknown. Spindle cell myxoid liposarcoma is another subtype of myxoid liposarcoma found in children. It behaves as a low-grade tumor, roughly similar to conventional myxoid liposarcoma (Alaggio et al. 2009).

So-called fibrohistiocytic tumors: *pleomorphic malignant fibrous histiocytoma/undifferentiated high-grade pleomorphic sarcoma*

Undifferentiated high-grade pleomorphic sarcoma (UHGPS), in the past called malignant fibrous histiocytoma (MFH), is a controversial entity characterized by pleomorphic spindle cells with fibroblastic and histiocytic differentiation. Its existence has been challenged, the morphologic features being common to a variety of poorly differentiated sarcomas (Fletcher 1992).

According to the 2002 WHO classification, MFH/UHGPS is a diagnosis of exclusion and should be reserved for those sarcomas without evidence of a specific lineage differentiation detected by available techniques. The diagnosis of MFH in childhood has always been rare, even in the pre-immunohistochemistry era; it comprised about 2–6% of all pediatric sarcomas, including angiomatoid fibrous histiocytoma (now classified separately as an intermediate soft tissue neoplasm of uncertain histogenesis) (Cole et al. 1993; Corpron et al. 1996). Like their adult counterpart, pediatric MFH can arise in sites previously irradiated or as second malignancies (especially after retinoblastoma) and may be associated with a family history of cancer. Histologically, pleomorphic lesions are composed of spindle cells arranged in fascicles or sheets, displaying a focal storiform pattern and scattered pleomorphic cells with hyperchromatic nuclei and atypical mitoses or multinucleated cells. Large aggregates of polygonal/epithelioid cells may be found in more aggressive tumors. Immunostains are helpful to exclude other diagnoses, the tumors being negative for lineage specific markers.

UHGPS are highly aggressive tumors with a high metastatic rate and an overall 5-year survival around 60–70%. Survival and metastases are related to tumor depth and size (Alaggio et al. 2010b).

44.1.3.3 Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors (MPNST) occur mainly in adults, and only 10–20% are diagnosed in the first two decades. Nevertheless, they represent one of the most frequent subtypes among pediatric NRSTS. In general MPNST are high-grade tumors, often arising in axial sites, characterized by uncertain prognosis. In about 21–67% of cases, MPNST arise in patients affected by neurofibromatosis type 1 (NF1), by malignant transformation of preexisting neurofibromas. The life-time risk of developing MPNST in NF1 patients has been estimated at 8–13%, as compared to 0.001% in the general population (Evans et al. 2002). The molecular mechanisms responsible for malignant transformation of neurofibromas and those involved in tumor progression in both sporadic and NF1-associated MPNST are largely unknown. NF1 is caused by mutation in the NF1 suppressor gene, located in chromosome band 17q11. It encodes the neurofibromin, a protein inhibiting p21-RAS. NF1 inactivation is not sufficient for malignant transformation and further genetic alterations are needed, most of them probably involving genes regulating cell cycle. In fact, several alterations in tumor suppressor genes playing a pivotal role in cell cycle, such as mutations

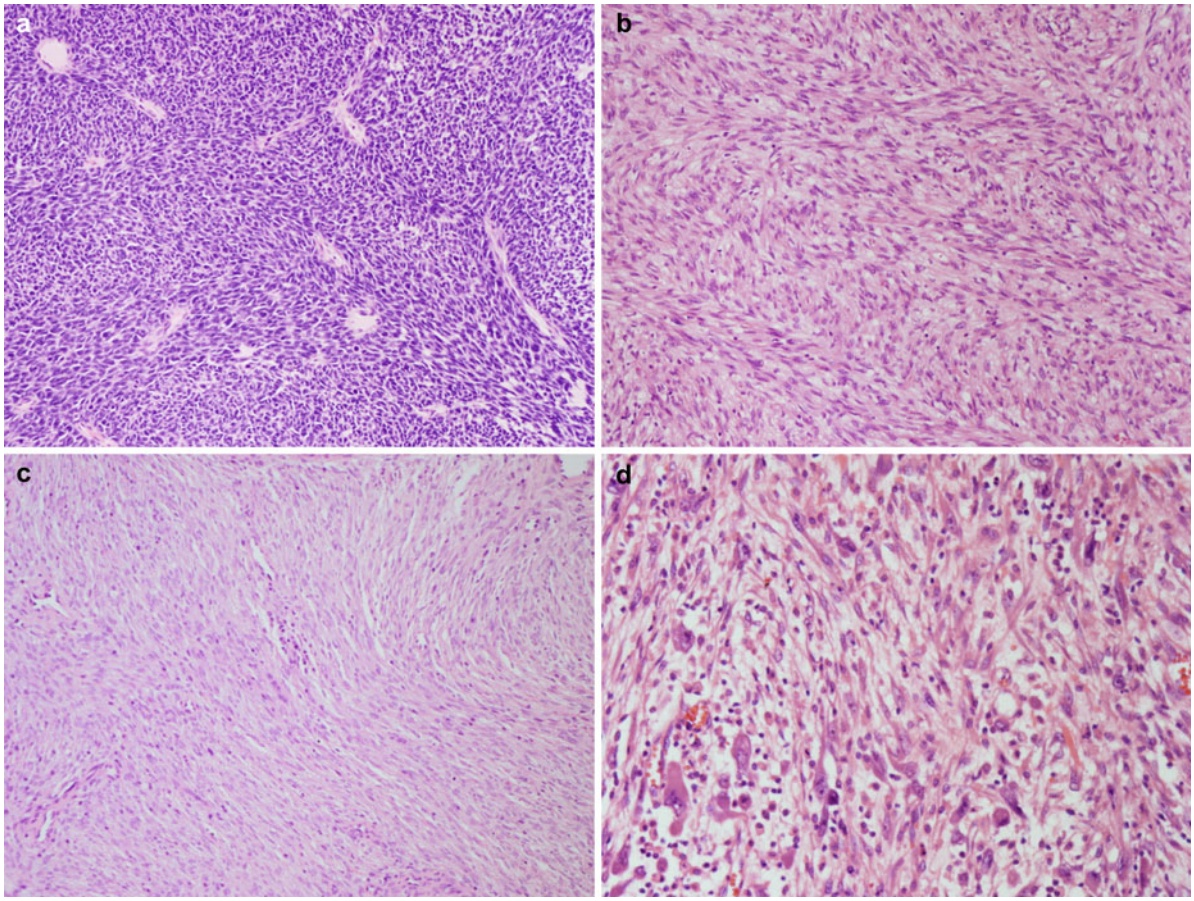

Fig. 44.5 Spindle cell sarcomas: (**a**) (HE staining, 100×) synovial sarcoma with the typical hemangiopericytomatous pattern; (**b**) (HE staining, 100×) malignant peripheral nerve sheath tumor (MPNST) showing fascicles of elongated cells with weavy nuclei; (**c**) (HE staining, 100×) congenital infantile fibrosarcoma with primitive elongated spindle cells; (**d**) (HE staining, 100×) inflammatory myofibroblastic tumor with elongated cells and scattered ganglion-like cells intermingled with lymphocytes and plasma cells

of TP53 and CDKN2A (p16INK4), have been reported in neurofibromas as they transform into MPNST (Ferrari et al. 2007a).

Histological diagnosis may be challenging, with the majority of MPNST highly cellular neoplasms mimicking other spindle cell sarcomas. At least focally the cells are arranged in sweeping fascicles, exhibit weavy nuclei typical of Schwann cells, and form palisades in about 10% of cases; other areas may be hypocellular with a myxoid stroma. Blood vessel shows a hyalinized wall, which is an important diagnostic tool. Criteria of malignancy are necrosis and mitotic activity. Immunostains show only rare S-100-positive cells (Fig. 44.5b). Morphologic variants of MPNST include epithelioid or glandular MPNST, respectively characterized by aggregates of epithelioid cells in solid nests or foci of glandular differentiation with mucin-secreting cells, rhabdoid MPNST, *triton tumor* (a MPNST with a rhabdomyosarcomatous component), and MPNST with a perineurioma-like component, showing a prominent perineurial differentiation. Unfortunately, in sporadic MPNST, there are no histologic markers predictive of clinical behavior and tumor grade does not appear to have a prognostic significance.

The Italian and German cooperative groups reported on a series of 167 pediatric MPNST cases (17% having NF1), with a 5-year overall survival and progression-free survival of 51% and 37%, respectively. Outcome was satisfactory only for the small group of resected and small tumors. NF1 patients have a peculiar poor outcome. That series confirmed the aggressiveness of MPNST, for which complete surgical resection is the mainstay of successful treatment. MPNST is generally regarded as a tumor with poor chemoresponsiveness, but in that series, an overall response rate to primary chemotherapy of 45% was recorded (Carli et al. 2005).

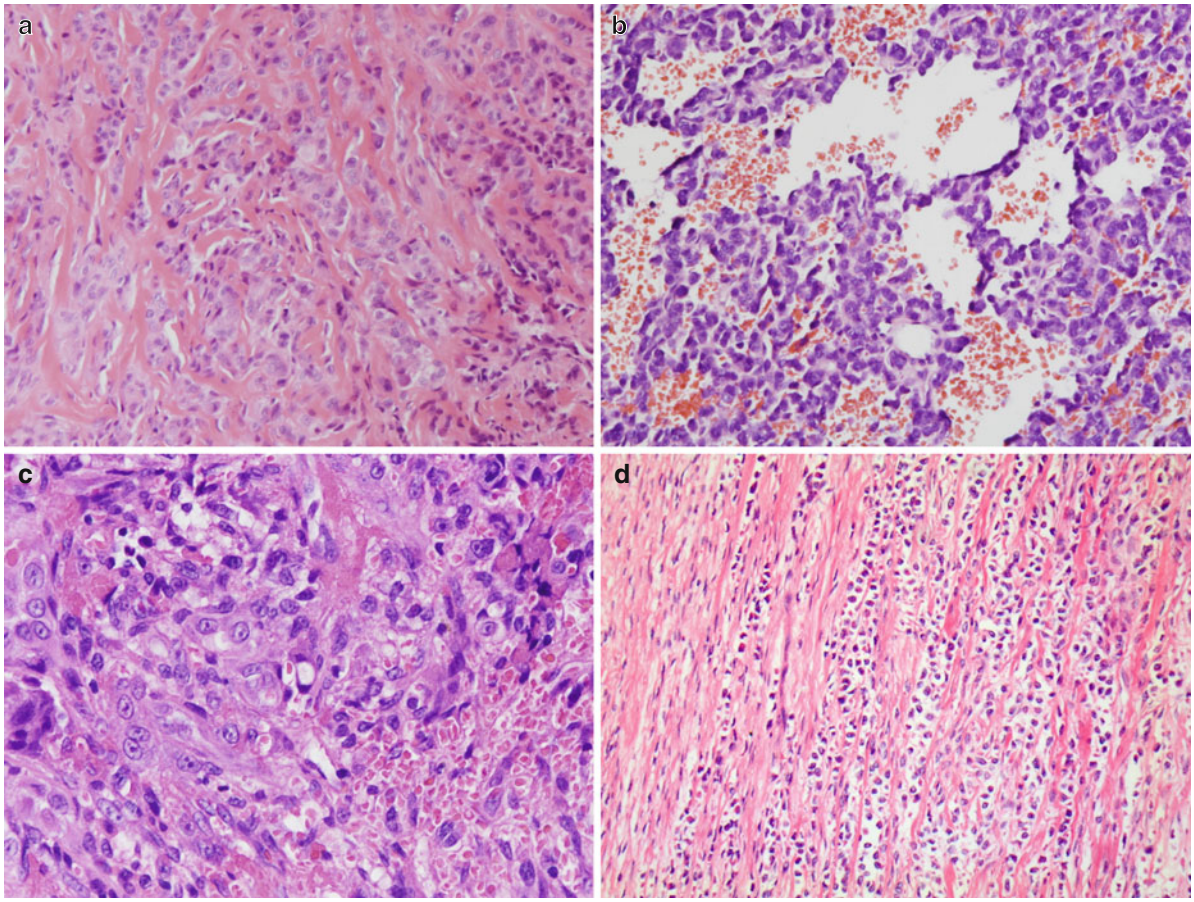

Fig. 44.6 Sarcomas with "epithelioid" cells: (**a**) (HE staining, 160×) epithelioid sarcoma showing large cells arranged in nests and cords embedded in a collagen stroma. (**b**) (HE staining, 100×) epithelioid sarcoma with vascular pattern mimicking epithelioid hemangioendothelioma. (**c**) (HE staining, 160×) epithelioid hemangioendothelioma with typical intracytoplasmic vacuoles, occasionally containing red cells. (**d**) (HE staining, 100×) Sclerosing epithelioid fibrosarcoma: cords of epithelioid in a collagen stroma. Fascicles of spindle cells with typical features of fibrosarcoma on the left

44.1.3.4 Malignant Tumors of Uncertain Differentiation

Epithelioid Sarcoma

Epithelioid sarcoma is a distinctive lesion, generally involving dermis or subcutaneous tissue, that may mimic clinically and morphologically a benign granulomatous process (Enzinger 1970). Peculiarly, it involves finger, hand, wrist, and forearm of adolescents and young adults. Lower extremities, shoulder, and less frequently trunk, head, and neck can be also involved. Epithelioid sarcoma may also occur in mucosal sites including the tongue and in genital areas (Casanova et al. 2006; Gross et al. 1996; Kodet et al. 1994). The tumors are slow-growing single or multiple ulcerating nodules of variable size. A particular tendency for lymph node involvement has been observed. The so-called proximal-type epithelioid sarcoma occurs in axial locations. It shares some morphological features with rhabdoid tumor and behaves more aggressively than conventional epithelioid sarcoma (Guillou et al. 1997b). Histologically, epithelioid sarcoma consists of nodular masses or large, eosinophilic polygonal cells imperceptibly merging with spindle cells. Cytologic atypia is minimal. Areas of central necrosis are frequent. Tumors may also show predominant spindle cells in a fibroma-like or dermatofibroma-like pattern or an angiomatoid angiosarcoma-like appearance with large epithelioid cells surrounding hemorrhagic spaces (Mirra et al. 1992; von Hochstetter et al. 1991) (Fig. 44.6a, b). Proximal-type epithelioid sarcoma shows prominent epithelioid cells with vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm.

Immunostains for low- and high-molecular-weight keratin, epithelial membrane antigen, and vimentin are generally positive. The majority of tumors express CD34 and CA 125. INI-1 negative staining in more than 50% of epithelioid sarcoma proximal-type supports a pathogenetic relationship with rhabdoid tumor (Chbani et al. 2009; Hornick et al. 2009).

Little information is available on clinical management in children. An Italian study reported on 30 patients <18 years old (19 classic-type and 11 proximal-type), suggesting a clinical course less aggressive than that generally observed in adults. In that series, 5-year event-free survival and overall survival rates were 62% and 92%, but overall survival dropped to 87% and 72% at 10 and 15 years, respectively. Local relapse was the major cause of treatment failure. The most significant finding influencing survival was tumor site (extremity location predicting a favorable outcome). A worse outcome was associated with the proximal-type variant. A response to chemotherapy was seen in 3/7 patients with measurable disease. The tendency for lymph nodal spread described in adults would be not clearly confirmed in pediatric cases (Casanova et al. 2006).

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) represents <1% of soft tissue sarcomas and occurs more frequently in patients younger than 40 years, often in the extremities and trunk (Folpe and Deyrup 2006). In children, it may arise in the head and neck (Casanova et al. 2000).

ASPS is characterized by a peculiar organoid pattern showing nests of epithelioid polygonal cells with eosinophilic cytoplasms, vesicular nuclei, and prominent nucleoli. PAS-positive intracytoplasmic rhomboid crystals are virtually diagnostic of ASPS. Immunostains are not helpful for diagnosis. The ASPSCR1–TFE3 fusion gene, deriving from chromosomal rearrangement at17q25 and Xp11.2, is typical of ASPS and is associated with a positive nuclear immunostaining for TFE3 (van Echten et al. 1995; Ladanyi et al. 2001; Argani et al. 2003).

Although tumor growth is slow and asymptomatic, ASPS is highly malignant with early vascular invasion and metastatic dissemination, more frequently to brain and lung. The elective treatment is a radical surgery, that generally allows a prolonged survival, but most of patients will ultimately succumb to disease. The role of chemotherapy is unclear; this entity is generally considered scarcely chemosensitive.

The ASPSCR1–TFE3 chimeric transcription factor induces the expression of numerous proteins that might represent therapeutic targets, including, among others, the Met, which is an angiogenetic factor, activating the downstream effectors AKT and MEK. A phase II clinical trial is currently accruing ASPS patients to evaluate the effect of a novel c-Met inhibitor, ARQ 197. Furthermore, several AKT and MEK inhibitors are also available, and using a multi-target therapeutic strategy might result in an improvement of prognosis. Overexpression of VEGF mRNA has also been identified in gene expression profiling of ASPS samples and may be a promising therapeutic target (Lazar et al. 2009; Tsuda et al. 2007).

Clear Cell Sarcoma of Tendons and Aponeuroses

Clear cell sarcoma (CCS), also called melanoma of soft parts, has a proclivity to involve tendons and aponeuroses of distal extremities of young individuals (Enzinger 1965). It has a close resemblance to melanoma and is characterized by fascicles and nests of pale, elongated, or epithelioid cells encased by delicate fibrous septa. The cells show clear cytoplasm frequently containing melanin, nuclei with prominent nucleoli. S-100 is generally positive. The cytogenetic hallmark is t(12;22)(q13;q12), resulting in a chimeric EWS/ATF1 gene, detected in about 75% of cases. The tumor has a prolonged clinical course with multiple local recurrences, late metastases, and a high rate of tumor deaths. Radical surgery is the elective treatment. Chemotherapy is generally considered ineffective. A series of 28 pediatric patients have been reported by the Italian and German Soft Tissue Sarcoma Cooperative Group, with survival rates around 60% (Ferrari et al. 2002). Gastrointestinal CCS-like tumor is a distinctive lesion morphologically resembling CCS, characterized by identical cytogenetic alterations, but lacking intracellular melanin and showing scattered osteoclast-like giant cells. The tumor is accompanied by prominent weight loss, anorexia, abdominal pain, bloody stools, and anemia. Although very few, pediatric gastrointestinal CCS behaves more aggressively. A prior history of acute lymphoblastic leukemia has been reported.

44.1.3.5 The PEComa Family Tumors

Perivascular-epithelioid cell tumors (PEComa) are a family of tumors sharing a common origin from a cell with an hybrid melanocytic and muscular phenotype,

lacking a normal counterpart. The different morphologic entities represented by angiomyolipomas, lymphangioleiomyomatosis, clear cell "sugar" tumor of the lung, clear cell myomelanocytic tumor of the falciform ligament/legamentum teres and abdomino-pelvic sarcoma of perivascular-epithelioid cells (PEC) show variation in their clinicopathologic features (Bonetti et al. 1992; Zamboni et al. 1996; Folpe et al. 2000b; Hornick and Fletcher 2006; Martignoni et al. 2007, 2008).

Angiomyolipomas may occur in the context of tuberous sclerosis complex (TSC) and arise in kidney, less frequently in liver (Goodman and Ishak 1984) or other sites (Hulbert and Graf 1983; Peh and Sivanesaratnam 1988; Castillenti and Bertin 1989; Watanabe and Suzuki 1999).

Classic angiomyolipomas are characterized by a variable combination of blood vessels with a hyalinized wall, smooth muscle and mature adipose tissue, whereas epithelioid AML display nests and sheets of large epithelioid cells (Eble et al. 1997; Mai et al. 1996; Martignoni et al. 1998). Lymphangioleiomyomatosis in children is exceptional (Nagy Nagy et al. 1998) and may occur in the context of TSC. It is characterized by multiple pulmonary nodules, composed of elongated cells surrounding small blood vessel, interstitial myoid cells, and ectatic lymphatics. Lymph nodes, retroperitoneum, and mediastinum may be also involved (Matsui et al. 2000; Torres et al. 1995). The nodules evolve into cystic lesions with destruction of the lung, pneumothorax, and pulmonary failure requiring lung transplant.

Only few "Sugar" tumors or clear cell tumors of the lung have been reported in children with identical clinical features as in adults. They generally occur as single benign nodules (Vijayabhaskar et al. 2010; Nehra et al. 2010; Kavunkal et al. 2007; Gora-Gebka et al. 2006), histologically composed of sheets or nests of large epithelioid cells with clear cytoplasm, and a prominent vascular network. Extrapulmonary sugar tumors have been also reported in children in breast, bone, and urethra. They differ from their pulmonary counterpart for the more frequent nuclear atypia, mitoses and necrosis.

Clear cell myomelanocytic tumor (CCMMT) is a variant of PEComa with a predilection for ligaments (ligamentum teres and falciform ligament) and extremities, characterized by fascicles of spindle cells with clear to eosinophilic cytoplasms (Folpe et al. 2000b). Abdominopelvic sarcoma is a malignant variant of PEComa, composed of sheets of epithelioid cells, with pleomorphism, necrosis, and vascular invasion (Bonetti et al. 2001). Immunohistochemistry plays a key role in the diagnostic work-up, disclosing the typical hybrid melanocytic (HMB45, Melan-A, tyrosinase, MiT family of transcription factors members, microphthalmia transcription factor-MiTF and TFE3), and muscular (smooth muscle actin, muscle-specific actin, sometimes calponin or h-caldesmon and less frequently Desmin) phenotype of cells (Pea et al. 1991).

Sporadic or TSC associated angiomyolipomas and other PEComas share common cytogenetic alterations. TSC is caused by malfunction of the TSC1/TSC2 complex, related to a somatic deletion in *TSC1 gene* (*on chromosome* 9q34) or inactivating mutations in *TSC1* or *TSC2* (on 16p13). In sporadic AML and PEComas, loss of heterozygosity of TSC2 gene is common (Pan et al. 2006, 2008). These genetic alterations activate the mTOR pathway promoting cell growth (Kenerson 2007; Wagner et al. 2010; Weinreb et al. 2007). Other genetic alterations include deletion of 1p, deletions on cr 19, chromosomal gain on 12q, 2q, 3q, 5 (Pan et al. 2006). Only a minority of PEComas carry a TFE3 gene fusion (Argani et al. 2010; Cho et al. 2008; Tanaka et al. 2009) and some of them have been reported in association with neuroblastoma.

The prognosis of PEComa is influenced by the histotypes. Classic angiomyolipomas are generally benign. Epithelioid angiomyolipomas of kidney metastasize in one-third of cases. The presence of at least three unfavorable prognostic features (atypical epithelioid cells representing at least 70% of the population, two or more mitotic figures/10 HPF, atypical mitoses or necrosis) appears to be predictive of a malignant behavior. Hepatic Epithelioid angiomyolipomas are generally benign. CCMMT showing a main diameter larger than 5 cm, infiltrative growth, hypercellularity, nuclear enlargement and hyperchromasia, high mitotic rate, atypical mitoses, and coagulative necrosis may have a more aggressive clinical behavior. PEComas are treated by complete surgical excision. Radiotherapy and chemotherapy are not effective. The use of the mTOR inhibitors, such as Sirolimus, may be an option in unresectable tumors (Subbiah et al. 2010).

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a rare neoplasm mainly affecting children and young adults with a male preponderance. Its classical histological

appearance, represented by solid sheets, nests, or cords of small cells in a desmoplastic stroma, can show many different morphological variations. Its specific immunohistochemical profile with divergent epithelial, muscular, and neural differentiation and the recurrent translocation t (11;22)(p13;q12), that gives rise to the fusion gene EWS-WT1, represent important diagnostic tools, especially when the typical clinicopathological features are lacking.

DSRCT occurs in the abdominal and pelvic cavity or in other sites in association with serosal surfaces such as paratesticular region and pleura. Rare examples of extra-serosal DSRCT involving parotid gland, posterior cranial fossa, bone and soft tissue, pancreas, and kidney have been also reported. In particular when arising in abdominal cavity, the tumor is often disseminated at onset, and is characterized by a dismal outcome, despite the various intensive multimodality treatment approaches (including aggressive surgery, intensive chemotherapy, and radiotherapy) attempted over the years (Kushner et al. 1996; Bisogno et al. 2010).

Extrarenal Rhabdoid Tumor

Malignant rhabdoid tumor is a highly aggressive neoplasm, mostly occurring in the central nervous system and kidney of infants and children. Less frequently, it may arise in somatic soft tissues, abdomen, pelvis, retroperitoneum, liver, heart, and gastrointestinal tract. The histologic diagnosis is generally straightforward when the tumor shows the typical morphology characterized by large epithelioid cells, with abundant eosinophilic or amphophilic cytoplasm containing juxtanuclear hyaline-like globules, large nuclei with prominent nucleoli and a polyphenotypic immunophenotype, with variable expression of Vimentin, EMA, cytokeratins, CD99, S-100, SMA. The identification of a recurrent genetic alteration in RT, in the region 11.2 of the long arm of chromosome 22 (22q11.2), characterized by the deletion or mutation of hSNF5/SMARCB1/INI1 gene resulting in the loss or reduced expression of INI protein, has contributed to enlarge the morphologic spectrum of rhabdoid tumor (Versteege et al. 1998; Weeks et al. 1989; Wick et al. 1995; Parham et al. 1994; Schofield et al. 1996). Rhabdoid tumors are very rare and very aggressive disease. These tumors are currently treated with intensive chemotherapeutic strategy (multidrug therapy with vincristine, ifosfamide, carboplatin, etoposide, doxorubicin, and cyclophosphamide), but improvements in genetic studies are strongly needed to cast light on their biology in order to think about new treatment approaches (Kodet et al. 1991).

Synovial Sarcoma

Synovial sarcoma is a tumor of uncertain histogenesis, accounting for 6–10% of adult soft tissue sarcomas and predominantly affecting children older than 10 years, adolescents, and young adults. It is the most frequent pediatric NRSTS (Sultan et al. 2009).

Histologically, this tumor is variously composed of spindle and epithelioid cells. Spindle cells are small, uniform, ovoid with pale nuclei, sparse cytoplasm, and inconspicuous cell borders. Epithelioid cells exhibit same nuclei and a more abundant cytoplasm (Fig. 44.5a). According to the different components, three major subtypes are recognized: the monophasic fibrous synovial sarcoma, composed of spindle cells with no evidence of epithelial component (the epithelial monophasic type is very rare and mimics an adenocarcinoma); the biphasic synovial sarcoma, containing spindle and epithelioid cells in variable proportions; the poorly differentiated synovial sarcoma, a highly cellular sarcoma resembling a small round cell tumor, whose diagnosis may be challenging. Synovial sarcoma express cytokeratins, in particular cytokeratins 7 and 19, which are not expressed in other sarcomas, epithelial membrane antigen, vimentin, CD99, and bcl2. Cytogenetic studies show chromosomal translocation t(X;18)(p11.2;q11.2). The SS18 (or SYT) gene from chromosome 18 is disrupted and juxtaposed to either SSX1, SSX2, or SSX4 on chromosome X, in a mutually exclusive manner. SYT-SSX1 may be associated with a biphasic histology and higher ki67 index. SYT-SSX2 is more frequently found in monophasic fibrous type (Mancuso et al. 2000; Mezzelani et al. 2001). Some studies suggest a better prognosis for tumors bearing the SYT-SSX1 transcript, but the prognostic significance of molecular findings is controversial (Guillou et al. 2004). The protein product of SMRRCB1/INI1 (INI1) gene, a tumor suppressor gene lost in malignant rhabdoid tumor, is reduced in the majority of synovial sarcoma. The specific molecular mechanism is not known and a post-transcriptional interaction of SS18-SSX transcript with the chromatin-remodeling pathway has been suggested. Moreover, gene expression studies are providing new insights into the molecular pathways involved in tumor progression in synovial sarcoma, including Wnt, IGF, ERBB2, HGF/MET, and beta-catenin pathways, disclosing new therapeutic

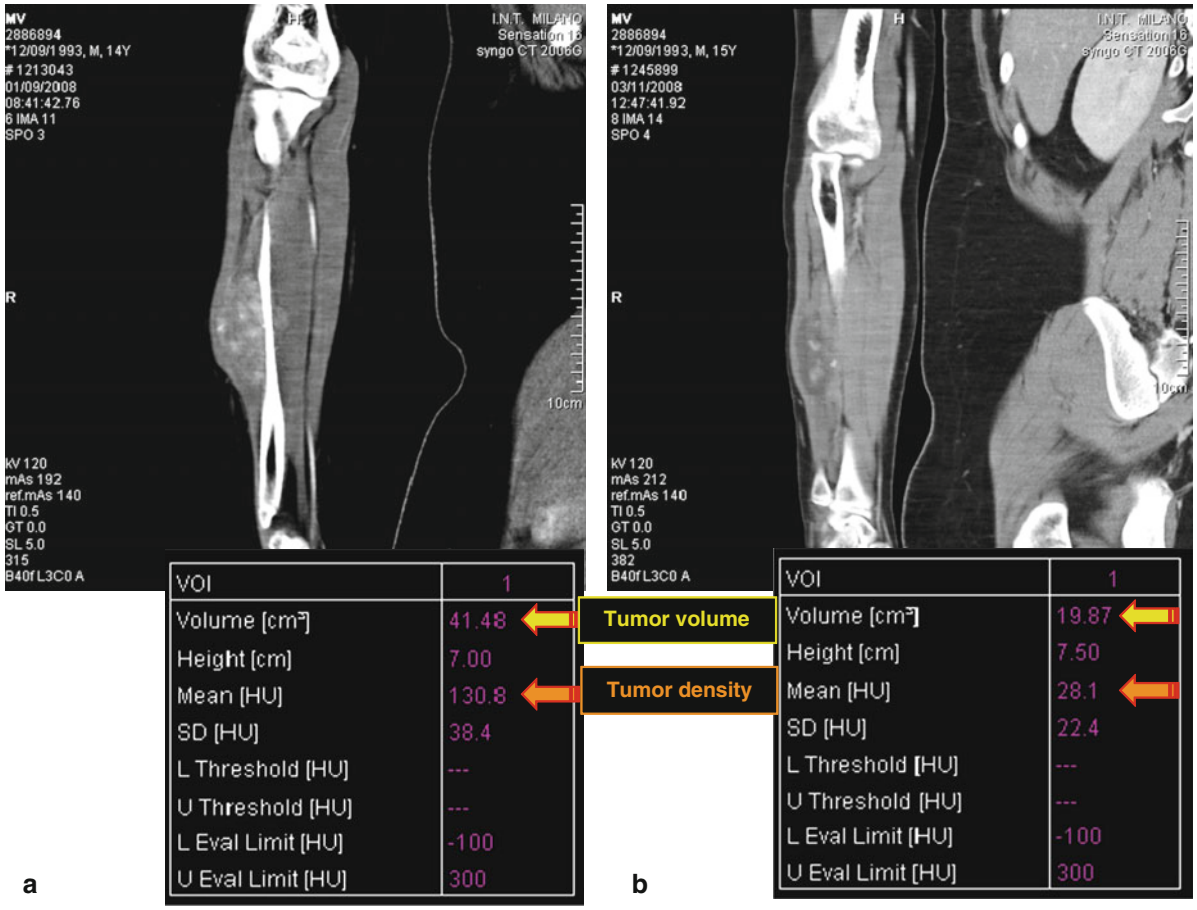

Fig. 44.7 Computed tomography scan of synovial sarcoma of the right forearm: (**a**) at onset, before chemotherapy; (**b**) after three courses of chemotherapy with ifosfamide and doxorubicin. Response to chemotherapy is shown by volume reduction as well as changes in tumor tissue characteristics (reduction of tumor density) (Courtesy Dr. Carlo Morosi, Radiology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy)

perspectives (Tamborini et al. 2004; Kawaguchi et al. 2005; Thomas et al. 2005).

Synovial sarcoma is the typical sarcoma subtype crosswise between the pediatric and adult age groups (Sultan et al. 2009). However, since up to recent times, different therapeutic strategies have been developed for pediatric and adult oncology protocols dealing with this tumor, in particular concerning the use of systemic therapy, though no published data describes a different biology of synovial sarcoma when arising in adults as opposed to children. Historically, relatively high rates of response to chemotherapy were recorded in pediatric series (i.e., an approximately 60% rate, that is higher than the response rate usually reported for other adult soft tissue sarcomas, but lower than that observed in rhabdomyosarcoma) (Fig. 44.7), and therefore, synovial sarcoma was traditionally considered as a "rhabdomyosarcoma-like" tumor by pediatric oncologists, particularly in Europe: Children were enrolled over the years in rhabdomyosarcoma protocols, thus receiving the same chemotherapy as for rhabdomyosarcoma patients, even in case of completely resected small tumors (Ferrari et al. 2008; Okcu et al. 2003; Brennan et al. 2010).

Differently, adult patients with synovial sarcoma were treated according to the same guidelines adopted for other soft tissue sarcomas; for instance, adjuvant chemotherapy was generally only used for those patients enrolled in randomized trials with a no-therapy control arm. Whether these different strategies produced differences in patient survival remains to be demonstrated; however, pediatric reported series showed 5-year survival rates of around 80%, which is higher than usually reported in

Table 44.4 Recent studies on pediatric synovial sarcoma

Pediatric synovial sarcoma series	
Okcu F, 2003 Multicenter study MDACC, SJCRH, INT Milan, CWS	219 pts <20 years 5-year OS 80% Rate of response to chemotherapy – 60%
Brecht IB, 2005 CWS, AIEOP-STSC	150 pts <18 years, IRS groups I-II (initial gross resection) Nearly all patients received chemotherapy 5-year OS 89% Identification of low-risk patients (group I, ≤5 cm) for which chemotherapy might be omitted
Ferrari A, 2009 AIEOP-STSC	115 patients <20 years 5-year OS 76.9%, worse outcome for non-extremity sites vs limbs (OS 55.1% vs 84.0%)
Brennan B, 2010 UK CCLG	77 patients <18 years 5-year EFS and OS 72% and 76% Prognostic factors: T stage and IRS group
Comparison pediatric vs adult series	
Ferrari A, 2004 INT Milan	271 patients of all ages (46 <17 years) 5-year OS 64% Role of adjuvant chemotherapy Age < 17 years: 78% received chemotherapy – 5-year EFS 66% Age ≥ 17 years: <20% received adjuvant CT – 5-year EFS ~ 35%
Sultan I, 2009 SEER (1983–2005)	1268 cases (213 ≤18 years) No major differences in stage distribution 5-year cancer-specific survival: 83% vs 62% (p<0.001) Multivariate analysis: significantly higher mortality for adults after adjusting for other variables

OS overall survival, *EFS* event-free survival, *IRS* Intergroup Rhabdomyosarcoma Study, *MDACC* M.D. Anderson Cancer Center, *SJCRH* St. Jude Children Research Hospital, *INT* Istituto Nazionale Tumori Milan, *CWS* Cooperative Weichteilsarkomen Studie (German Soft Tissue Sarcoma Cooperative Group), *AIEOP-STSC* Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee (Italian Cooperative Group), *UK CCLG* United Kingdom Children's Cancer and Leukaemia Group, *SEER* Surveillance, Epidemiology, and End Results

adult series (Lewis et al. 2000; Trassard et al. 2001). A recent study on the large cohort of synovial sarcoma cases registered in the SEER database (1983–2005) highlighted that the cancer-specific mortality was higher in adults than in children (34% vs 16%, respectively), and the outcome remained consistently worse for adults when the analysis was adjusted for the different prognostic variables (i.e., tumor size, site, and stage), suggesting that factors other than the possible difference in the incidence of unfavorable clinical variables might be involved in the unsatisfactory outcome for adult cases (Sultan et al. 2009). The hypothesis that the different treatment results might be related, at least in part, to the different treatment strategies adopted (i.e., the different use of chemotherapy) would be supported by the retrospective study of the Istituto Nazionale Tumori in Milan (on patients of all ages), in which adjuvant chemotherapy (administered to most of the children and to a minority of the older patients) seemed to improve patient outcome (Ferrari et al. 2004) (Table 44.4).

In recent years, the management of synovial sarcoma patients seems to be changing to some degree in both pediatric and adult cases, tending to converge toward a common strategy (Ferrari 2009). Pediatric oncologists have taken suggestions from adult experiences and moved toward a treatment concept partially similar to that adopted in the adult setting: The ifosfamide-doxorubicin chemotherapy is currently adopted as standard regimen, and its indication is given according to the patient's risk stratification, based on tumor size and site and surgical stage; in low-risk patients (completely resected tumors under 5 cm in size), chemotherapy is omitted (Brecht et al. 2006) (Fig. 44.2). On the other hand, adult oncologists seem to be recognizing that synovial sarcoma may be quite different from other adult

soft tissue sarcomas, particularly in the light of its higher chemosensitivity, probably standing midway between that of the most typical adult histotypes and that of pediatric small round cell tumors, such as rhabdomyosarcoma. Despite the absence of a published proof of its efficacy, in day-to-day clinical practice, many adult oncologists generally recommend chemotherapy for synovial sarcoma patients, not only in cases of advance disease, but also as an adjuvant treatment after surgery (Canter et al. 2008; Eilber et al. 2007).

44.1.3.6 Future Perspectives: Targeted Therapies

The management of adult soft tissue sarcomas (and therefore also of NRSTS) is currently entering the "histology-driven therapy era" (Ferrari 2008). Various drugs other than the classic ifosfamide-doxorubicin regimen have proved effective in particular histotypes, e.g., taxanes in angiosarcoma (Penel et al. 2008), gemcitabine and gemcitabine ± docetaxel in leiomyosarcoma (Hensley et al. 2002; Maki et al. 2007), and trabectidine in liposarcoma (Grosso et al. 2007). In particular, trabectidine has recently shown important activity in myxoid/round cell liposarcoma, possibly with a direct effect on the products of the histotype-specific FUS-CHOP translocation: After many years without any effective new drugs being registered, trabectidine has been officially approved by the European Agency for the Evaluation of Medicinal Products (EMEA) for the second-line treatment of adult soft tissue sarcomas.

The better understanding of the molecular pathways involved in tumor growth and progression is currently leading to the identification of new potential therapeutic targets: The product of the specific chromosomal translocations occurring in NRSTS may be perfect targets for new molecular agents specifically designed to influence the tumor's biology. New targets can be subdivided into signaling elements involved in cell cycle regulation and apoptosis, molecules responsible for tumor neoangiogenesis, and factors providing connective tissues disruption and tumor spread.

Several targeted therapies are currently under evaluation. Apart of GIST, imatinib has proven effective against dermatofibrosarcoma protuberans (possibly by deregulating the platelet-derived growth factor-B (PDGF-B) resulting from the specific t(17,22) translocation) (McArthur et al. 2003), chordoma (Casali et al. 2004), and desmoid-type fibromatosis (Heinrich et al. 2006).

Preliminary interesting data are available on the effects of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) inhibitors as pazopanib (an oral angiogenesis inhibitor), in particular, in vascular sarcomas, leiomyosarcoma, and synovial sarcoma (Sleijfer et al. 2009).

The activities of the mTOR inhibitor rapamycin (a macrolide antibiotic) and its synthetic derivatives sirolimus, temsirolimus, everolimus, and ridaforolimus have been variously explored, since the phosphatidylinositol-3 kinase (PI3K)-Akt-mTOR pathway has a central role in cell growth and has been shown to be activated at various levels in many sarcomas (Chawla et al. 2007; Mita et al. 2008; Blay 2011). Eribulin mesylate (a tubulin-targeting synthetic analogue of halichondrin B) showed promising activity in leiomyosarcoma and adipocytic sarcomas (Schoffski et al. 2010). Other promising agents are the recombinant human monoclonal antibodies to the insulin-like growth factor 1 receptor (IGF1R) (Patel et al. 2010).

44.2 Rare Bone Tumors

Stefano Ferrari and Andrea Ferrari

Less than 0.2% of the malignant tumors are primary bone neoplasms. Though they are rare tumors, osteosarcoma and Ewing sarcoma are tumor types typical of children and adolescents, and their clinical management is usually well known by pediatric oncologists. Chondrosarcoma is typically a tumor of the adulthood and is very rare in pediatric age.

A wide variety of benign or locally aggressive tumors may affect bone in children: These entities can be classified into different categories according to the matrix, or substance, that they produce: i.e., osteoid – or bone-forming tumors, cartilage-forming tumors, fibrous lesions. Many cases are discovered incidentally; in other cases, they present with localized pain, swelling, deformity, or pathologic fracture. These tumors have characteristic radiographic features (i.e., type of periosteal reaction, calcification, well-defined or sclerotic border, lack of destruction of the cortex, and soft tissue extension) and can be diagnosed with plain radiographs: The evaluation of expert radiologists may avoid in many cases unnecessary invasive diagnostic studies. It is important to refer these cases to experienced orthopedic surgeon: Most cases can be managed

with observation. Curettage and bone grafting or excision may be required in more aggressive cases (Yildiz et al. 2003; Wyers 2010).

However, it is very important to consider that patients with enchondromatoses or multiple osteochondromas have a higher risk of developing chondrosarcoma.

44.2.1 Chondromas

Enchondroma may be observed in children, young, and adults. It is usually asymptomatic and the diagnosis may be made after imaging investigation performed for other reasons. Most of the cases are observed in the tubular bones of the hand, where enchondroma is the most frequent bone tumor. Other preferred location are the long bones (especially the femur). Enchondroma can reach considerable extension in the major long bones and may cause pathologic fractures.

The neoplasm is frequently central, sometimes eccentric or intracortical. It is an osteolysis, with rounded, lobulated, well-defined edges with a thin rind of reactive sclerosis. Usually the lesion contains granular, popcorn, ring-like opacities that represent calcification and ossification at the periphery of the lobules. The computed tomography scan shows a radio-dense lobular or multi-islands lesion with sharp limits and a clear lack of permeative alterations of the cortex. The pathology appearance is characterized by lobules of cartilage with the typical aspect of hyaline cartilage. The calcified areas appear as granules white-opaque. The chondrocytes are sparse, with small, round, dense nuclei, of relatively uniform size. Diagnosis can usually be made on the basis of the clinico-radiographic features. The majority of enchondromas do not require biopsy nor surgical treatment, and patients should be followed up by means of standard radiography.

Periosteal chondroma is a benign hyaline cartilage neoplasm of bone surface that arises from the periosteum. It prefers the metaphyses of the long bones, particularly the proximal humerus. It may be painful and some swelling can be observed. The imaging shows a superficial erosion of the bone cortex with regular borders. Such erosion is caused by an hemispherical parosteal cartilaginous mass, usually of small-to-moderate size. In the largest chondromas, the tumor often contains granular or popcorn densities. Histologically, the tumor is very similar to enchondroma, but more frequently it displays features of cell proliferation (high cellularity, nuclear plumpness, and frequent double nucleated cells). Being somewhat painful and causing some swelling in most instances, it usually requires surgical management consisting of either en-bloc marginal excision or thorough curettage (Boriani et al. 1983).

44.2.1.1 Enchondromatoses (Ollier Disease, Maffucci Syndrome)

Enchondromatoses are rare; patients are younger than those with solitary tumors, the majority presenting during the first two decades of life. It has been reported that age at presentation is inversely related to the severity of the disease. *Ollier disease* is a developmental disorder characterized by failure of normal enchondral ossification and production of cartilaginous masses (enchondromas) leading to bone deformity. There is predominant unilateral involvement. *Maffucci syndrome* combines the features of Ollier disease associated with multiple soft tissue hemangiomas.

The most affected bones are the small tubular bones of the hand and foot, but the enchondromas may present everywhere in the skeleton. Swelling, deformities, and lower limb length discrepancy (even >10 cm) are the dominant symptoms.

Chondrosarcomas may develop in both syndromes (in approximately 25% of cases, after the age of 20–40 years), and there is an increased risk of extraskeletal malignancies, such as breast, liver, ovarian cancers and brain tumors.

Surgical treatment is aimed to relieve symptoms, rather than excise the enchondromas. Skeletal deformities and limb length discrepancy are addressed by osteotomies and/or lengthening procedures. Prognosis is burdened by the incidence of malignant change (Liu et al. 1987; Albregts and Rapini 1995; Altay, et al. 2007; Silve and Juppner 2006).

44.2.1.2 Multiple Osteochondromas

Osteochondroma (osteocartilaginous exostosis) is a cartilage-capped bony projection arising on the external surface of bone containing a marrow cavity that is continuous with that of the underlying bone. Osteochondroma is not a neoplasm, but, especially the poliostotic presentation, can go toward a malignant transformation. The diagnosis of osteochondroma is usually performed in the pediatric age with a prevalence for the male gender. The most frequent localization is in the metaphysic of long bones: distal femur, proximal humerus, and proximal tibia.

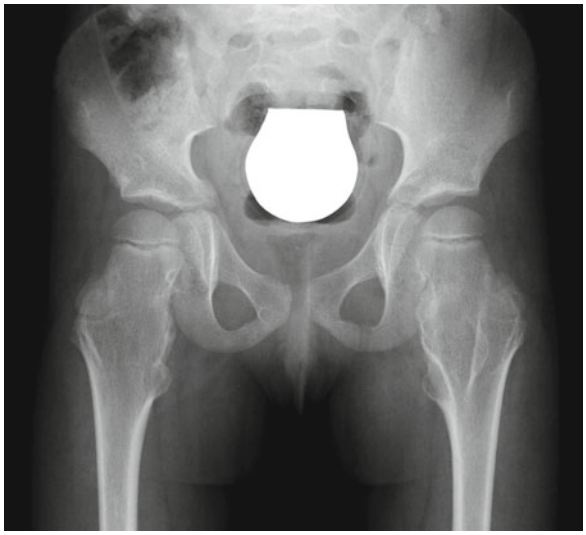

Fig. 44.8 Multiple osteochondromas in a 4-year-old girl (Courtesy Dr. Annette Schmitz-Stolbrink, Pediatric Radiology, Dortmund, Germany)

Multiple osteochondromas is an autosomal dominant condition. It is genetically heterogeneous and is caused by mutations in one of the exostosin (EXT) genes, tumor suppressor genes located respectively at 8q24 and 11p11-p12 (Fig. 44.8). The most important complication of this condition is the malignant transformation in chondrosarcoma. A cartilage cap >1.5 cm, as evaluated by means of magnetic resonance imaging, should be regarded with caution as a possible radiographic marker of malignant transformation (Bovee 2008; Ahmed et al. 2003).

44.2.1.3 Chondrosarcoma

Primary chondrosarcoma is a tumor of adulthood and old age. The majority of patients are older than 50 years with a peak incidence in the fifth to the seventh decades of life. Chondrosarcomas are graded on a scale of 1–3 (based on nuclear size, nuclear staining, and cellularity), from moderately cellular tumors similar to enchondroma to pleomorphic and atypical lesion with high mitotic rate. The majority of primary chondrosarcomas are grade 1 or 2.

Secondary chondrosarcoma arises from in a benign precursor, either osteochondroma or enchondroma. The risk of developing chondrosarcoma has been reported around 2% for solitary osteochondroma and 10–25% for multiple osteochondromas 5–25%. Patients with secondary chondrosarcoma are generally younger than patients with primary tumor. The pelvic and shoulder girdle bones are frequently affected. Changes in symptoms (sudden pain, increase in swelling) and radiological findings (increased thickness of the cartilage cap, destructive permeation of bone, development of soft tissue mass) in a patient with a known precursor lesion herald the development of chondrosarcoma. Secondary chondrosarcomas are generally low-grade tumors.

44.2.1.4 Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma (MCS) is a rare malignancy characterized by a biphasic histologic pattern of small undifferentiated round cells intermixed with islands of well-differentiated cartilaginous matrix. Because of its aggressive clinical behavior, MCS should be always regarded as a high-grade sarcoma.

MCS is a rare tumor. In comparison to the most frequent classic chondrosarcoma, generally affecting patients who are >50 years old, MCS typically occurs in young adults, it is highly malignant, and has a high proportion of extraskeletal tumors (about one-third of MCS occur in soft tissues, whereas extraosseous classic chondrosarcoma account for <1% of all cases). In the SEER database (1973–2006), only 24 children with MCS are recorded (and 142 adults). Tumor locations are bone and joints ($n=9$), soft tissue ($n=7$), nose/nasal cavity ($n=2$), eye/orbit (3), cranial nerves (1), lung (1), and kidney (1).

A German retrospective study reported on 15 cases aged 0–25 years, 4 osseous and 11 extraosseous. Tumor sites were head/neck (6 cases), paravertebral (3), pelvis (3), limbs (2), and kidney (1). Actuarial 10-year event-free and overall survival rates were 53% and 67%, respectively (Dantonello et al. 2008). Emerging cytogenetic data have raised the idea that this tumor may be closely related to extraskeletal Ewing's sarcoma/peripheral primitive neuroectodermal tumors (pPNET); patients with MCS should be probably treated with multimodal regimens, following Ewing's sarcoma protocols.

44.2.1.5 Chondroblastoma

Chondroblastoma is a benign rare tumor of the second decade of life, usually epiphyseal, located distally in long bones. Pain is usually present and, relatively common, also joint effusion. The radiographic appearance is characterized by a round or oval radiolucent lesion, small-to-moderate in size within the epiphysis or an apophysis or even extending across the plate. The

margins are sharp with a sclerotic rim. The cortex may be expanded but preserved in most cases. Usually no periosteal reaction can be detected. Calcification inside the defect is observed in 30–40% of cases.

Histologically, chondroblastoma shows a combination of mononuclear cells and giant cell. The typical cell is uniform, round to polygonal cell with well-defined cytoplasmic borders, clear to slightly eosinophilic cytoplasm, and a round to ovoid nucleus (chondroblasts). Chondroblasts are packed in pseudo-lobulated sheets often showing a pavement-like pattern.

Chondroblastoma has a slow course and may be surgically treated with curettage. The incidence of local recurrence is <20% and is related to the site of the tumor. Lung metastases can exceptionally complicate the course of the disease, but they can be effectively surgically removed.

44.2.1.6 Chondromyxoid Fibroma

Chondromyxoid fibroma is a benign tumor made by lobulated, fibromyxoid, and chondroid tissue, typical of the second and third decades of life, arising in the metaphysis of long bones (preferred sites are the proximal tibia). Mild-to-moderate pain is generally associated with local swelling. Radiographically, it appears as a small, metaphyseal and eccentric radiolucent defect, usually with the long axis parallel to the bone of origin, sharply marginated for a sclerotic rim. There may be cortical destruction with extension to the soft tissue with absent or minimal periosteal reaction (Fig. 44.9).

44.2.1.7 Osteoblastoma

Osteoblastoma is a benign tumor, made of osteoblasts producing osteoid and woven bone, arising in the second to third decades with an evident predilection for the posterior arch of the vertebral column and the sacrum. Signs of root compression may be present. Osteoblastoma is an osteolytic tumor well circumscribed and confined by a shell of reactive bone. Most of the tumors are of small size. In larger tumors, cystic spaces can be detected with radiographic appearance similar to an aneurismal bone cyst. Microscopically, the tumor consists of large osteoblasts producing osteoid and woven bone spicules and thin trabeculae. The surgical curettage is curative in most of the lesions. In selective cases, arterial embolization may be useful to reduce hemorrhage during surgery and postoperative radiation therapy can be added to improve the local control (Greenspan 1993).

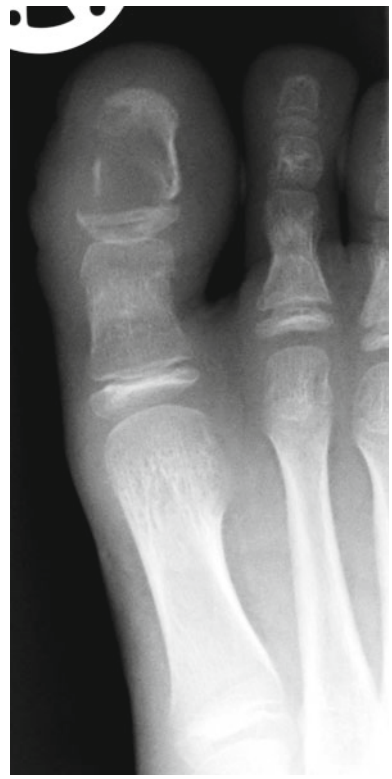

Fig. 44.9 X-ray of a chondromyxoid tumor of the toe in a 12-year-old boy (Courtesy Dr. Annette Schmitz-Stolbrink, Pediatric Radiology, Dortmund, Germany)

44.2.1.8 Osteoid Osteoma

Osteoid osteoma is a small benign tumor, made of osteoid and woven bone, surrounded by reactive bone. The tumor usually affects patients in the pediatric age. It mainly occurs in the appendicular skeleton (femur in particular), while it is rare in the trunk, with the exception of the spine (mostly localized in the posterior arch). The almost constant symptom is pain, with a typical tendency to increase during the night, relieved by nonsteroidal anti-inflammatory drugs. When localized near a joint, limited motion and chronic synovitis can be observed. In the spine, it may cause muscular spasm with stiff scoliosis. The basic radiographic element is a small (1–2 cm) rounded area of osteolysis ("nidus"), surrounded by a halo of bone sclerosis.

Left untreated it increases very slowly. Surgery, up to late 1990s, has been historically the mainstay of treatment. Nowadays computed tomography-guided percutaneous radiofrequency or laser ablation is considered the treatment choice. Success rate of this approach is usually more than 90% based on pain

relief. Surgery remains an option in cases refractory to percutaneous ablation (Kaweblum et al. 1993; Kneisl and Simon 1992).

44.2.2 Giant Cell Tumor of Bone

Giant cell tumor of bone is a relatively rare tumor (high incidence rates are reported in Asia) characterized by a benign but locally aggressive behavior. Rare cases of metastases are reported, as well as transformations to a malignant sarcoma phenotype. Giant cell tumor of bone usually affects young female, arising in long bones. The tumor presents as an osteolytic lesion, characterized by the presence of multinucleated giant cells (osteoclast-like cells) and stromal cells that express RANK ligand, a key mediator of osteoclastic activation. Radiologically, the tumor may show a non-sclerotic and sharply defined border, and a characteristic "soap bubble" appearance. Substantial skeletal morbidity may occur. Surgery is the treatment of choice. In unresectable cases, therapy with bisphosphonates may be used in order to induce apoptosis and prevent osteolysis. More recently, denosumab (a monoclonal antibody targeting the RANK ligand) showed to be significantly active (86% of tumor response was reported in a phase II trial on 37 patients with recurrent or unresectable disease) and may represent a potentially important treatment option (Thomas and Skubitz 2009; Thomas et al. 2010; Balke and Hardes 2010).

44.2.2.1 Adamantinoma

Adamantinoma is a slow-growing primary malignant tumor of long bone. The tumor may be characterized by a wide range of morphological patterns, the most common of which consists of circumscribed masses or tubular formations of what appear to be epithelial cells surrounded by spindle-celled fibrous tissue. Immunohistochemically, the epithelial cells show coexpressions of keratin, especially basal epithelial cell keratins (CKs 5, 14 and 19) and vimentin. The cells of origin and the pathogenesis of the disease are still unknown (Qureshi et al. 2000).

Adamantinoma is a very rare disease. Though the real number of cases may be underestimated in a cancer registry, only 15 cases under 20 years of age and 42 older cases are reported in the SEER database (1973–2006). A comprehensive literature review was able to identify 119 pediatric cases (Van Rijn et al. 2006).

The term "adamantinoma" derives from the Greek word "adamantinos," that means "very hard." The typical presentation of adamantinoma is a painless swelling on the anterior side of the tibia. On conventional imaging, adamantinoma initially appears as a cortical lytic lesion without significant periosteal reaction, but in advanced cases the tumor consists of a bubbly multiloculated sharply delineated lesion, with cortex disruption and soft tissue component.

Surgery is the mainstay of treatment. However, tumors may present in advanced stage and conservative wide resection with free margins is often unfeasible. Amputation might be required in more aggressive cases. Chemotherapy and radiotherapy do not have a role in the treatment of this tumor. The overall outcome is relatively good. In the pediatric review (Van Rijn et al. 2006), 13% of cases developed metastases (mainly in the lungs), and 10% of cases died of tumor. However, amputation was necessary in around 30% of cases.

References

Ahmed AR, Tan TS, Unni KK et al (2003) Secondary chondrosarcoma in osteochondroma: report of 107 patients. Clin Orthop Relat Res 411:193–206

Alaggio R, Ninfo V, Rosolen A, Coffin CM (2006) Primitive myxoid mesenchymal tumor of infancy: a clinicopathologic report of 6 cases. Am J Surg Pathol 30:388–394

Alaggio R, Coffin CM, Weiss SW et al (2009) Liposarcomas in young patients: a study of 82 cases occurring in patients younger than 22 years of age. Am J Surg Pathol 33:645–658

Alaggio R, Cecchetto G, Bisogno G et al (2010a) Inflammatory myofibroblastic tumours in childhood: a report from the Italian Cooperative Group studies. Cancer 116:216–226

Alaggio R, Collini P, Randall RL et al (2010b) Undifferentiated high-grade pleomorphic sarcomas in children: a clinicopathologic study of 10 cases and review of literature. Pediatr Dev Pathol 13:209–217

Albregts AE, Rapini RP (1995) Malignancy in Maffucci's syndrome. Dermatol Clin 13:73

Allen PW (1977) The fibromatoses: a clinicopathologic classification based on 140 cases. Am J Surg Pathol 1:255–270, and 305–321

Altay M, Bayrakci K, Yildiz Y et al (2007) Secondary chondrosarcoma in cartilage bone tumors: report of 32 patients. J Orthop Sci 12:415

Antonescu CR, Rosenblum MK, Pereira P et al (2001) Sclerosing epithelioid fibrosarcoma: a study of 16 cases and confirmation of a clinicopathologically distinct tumor. Am J Surg Pathol 25:699–709

Argani P, Lal P, Hutchinson B et al (2003) Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. Am J Surg Pathol 27:750–761

Argani P, Aulmann S, Illei PB et al (2010) A distinctive subset of PEComas harbors TFE3 gene fusions. Am J Surg Pathol 34:1395–1406

Balke M, Hardes J (2010) Denosumab: a breakthrough in treatment of giant-cell tumour of bone? Lancet Oncol 11:218–219

Belarezo FS, Joshi VV (2002) Proliferative and neoplastic disorders in children with acquired immunodeficiency syndrome. Adv Anat Pathol 9:360–370

Bernstein R, Zeltzer PM, Lin F, Carpenter PM (1994) Trisomy 11 and other nonrandom trisomies in congenital fibrosarcoma. Cancer Genet Cytogenet 78:82–86

Billings SD, Giblen G, Ganburg-Smith JC (2005) Superficial low-grade fibromyxoid sarcoma (Evans tumor): a clinicopathologic analysis of 19 cases with a unique observation in the pediatric population. Am J Surg Pathol 29:204–210

Bisogno G, Ferrari A, Rosolen A et al (2010) Sequential intensified chemotherapy with stem cell rescue for children and adolescents with desmoplastic small round-cell tumor. Bone Marrow Transplant 45:907–911

Blay JY (2011) Updating progress in sarcoma therapy with mTOR inhibitors. Ann Oncol 22(2):280–287

Bonetti F, Pea M, Martignoni G, Zamboni G (1992) PEC and sugar tumor. Am J Surg Pathol 16:307–308

Bonetti F, Martignoni G, Colato C et al (2001) Abdominopelvic sarcoma of perivascular epithelioid cells. Report of four cases in young women, one with tuberous sclerosis. Mod Pathol 14:563–568

Bonvalot S, Eldweny H, Haddad V et al (2008) Extra-abdominal primary fibromatosis: aggressive management could be avoided in a subgroup of patients. Eur J Surg Oncol 34:462–468

Boriani S, Bacchini P, Bertoni F, Campanacci M (1983) Periosteal chondroma. A review of twenty cases. J Bone Joint Surg Am 65:205

Bourgeois JM, Knezevich SR, Mathers JA, Sorensen PH (2000) Molecular detection of the ETV6-NTRK3 gene fusion differentiates congenital fibrosarcoma from other childhood spindle cell tumors. Am J Surg Pathol 24:937–946

Bovee JV (2008) Multiple osteochondromas. Orphanet J Rare Dis 3:3

Bramwell VHC (2001) Adjuvant chemotherapy for adult soft tissue sarcoma: is there a standard of care? J Clin Oncol 19: 1235–1237

Brecht IB, Ferrari A, Int-Veen C et al (2006) Grossly-resected synovial sarcoma treated by the German and Italian pediatric soft tissue sarcoma cooperative group: discussion on the role of adjuvant therapies. Pediatr Blood Cancer 46:11–17

Brennan B, Stevens M, Kelsey A, Stiller CA (2010) Synovial sarcoma in childhood and adolescence: a retrospective series of 77 patients registered by the Children's Cancer and Leukaemia Group between 1991 and 2006. Pediatr Blood Cancer 55:85–90

Bridge JA, Kanamori M, Ma Z et al (2001) Fusion of the ALK gene to the clathrin heavy chain gene, CLTC, in inflammatory myofibroblastic tumor. Am J Pathol 159:411–415

Canter RJ, Qin LX, Maki RG et al (2008) A synovial sarcoma-specific preoperative nomogram supports a survival benefit to ifosfamide-based chemotherapy and improves risk stratification for patients. Clin Cancer Res 14:8191–8197

Carli M, Ferrari A, Mattke A et al (2005) Malignant peripheral nerve sheath tumours in pediatric age: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. J Clin Oncol 23:8422–8430

Casali PG, Messina A, Stacchiotti S et al (2004) Imatinib mesylate in chordoma. Cancer 101:2086–2097

Casanova M, Ferrari A, Bisogno G et al (2000) Alveolar soft part sarcoma in children and adolescents: a report from the Soft-tissue Sarcoma Italian Cooperative Group. Ann Oncol 11:1–5

Casanova M, Ferrari A, Collini P et al (2006) Epithelioid sarcoma in children and adolescents: a report from the Italian Soft Tissue Sarcoma Committee. Cancer 106:708–717

Castillenti TA, Bertin AP (1989) Angiomyolipoma of the spermatic cord: case report and literature review. J Urol 142: 1308–1309

Cessna MH, Zhou H, Sanger WG et al (2002) Expression of ALK1 and p80 in inflammatory myofibroblastic tumor and its mesenchymal mimics: a study of 135 cases. Mod Pathol 15:931–938

Chawla SP, Tolcher AW, Staddon AP et al (2007) Survival results with AP23573, a novel mTOR inhibitor, in patients with advanced soft tissue sarcomas: update of a phase II trial. J Clin Oncol 25:18S (Abstract 10076)

Chbani L, Guillou L, Terrier P (2009) Epithelioid sarcoma: a clinicopathologic and immunohistochemical analysis of 106 cases from the French sarcoma group. Am J Clin Pathol 131:222–227

Chen ST, Lee JC (2008) An inflammatory myofibroblastic tumor in liver with ALK and RANBP2 gene rearrangement: combination of distinct morphologic, immunohistochemical, and genetic features. Hum Pathol 39:1854–1858

Chibon F, Lagarde P, Salas S et al (2009) Molecular signature of metastasis outcome in sarcomas. Proceedings of the 100th annual meeting of the American Association for cancer research. AACR, Denver/Philadelphia, 2009. Abstract nr 4983

Cho HY, Chung DH, Khurana H et al (2008) The role of TFE3 in PEComa. Histopathology 53:236–249

Chung EB, Enzinger FM (1976) Infantile fibrosarcoma. Cancer 38:729–739

Chung EB, Enzinger FM (1981) Infantile myofibromatosis. Cancer 48:1807–1818

Coffin S, Boccon-Gibod L (2004) Fibroblastic- myofibroblastic proliferations of childhood and adolescents. Ann Pathol 24:605–620

Coffin CM, Jaszcz W, O'Shea PA, Dehner LP (1994) So-called congenital-infantile fibrosarcoma: does it exist and what is it? Pediatr Pathol 14:133–150

Coffin CM, Watterson J, Priest JR, Dehner LP (1995) Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol 19:859–872

Coffin CM, Dehner LP, Meis-Kindblom JM (1998a) Inflammatory myofibroblastic tumor, inflammatory fibrosarcoma, and related lesions: an historical review with differential diagnostic considerations. Semin Diagn Pathol 15:102–110

Coffin CM, Humphrey PA, Dehner LP (1998b) Extrapulmonary inflammatory myofibroblastic tumor: a clinical and pathological survey. Semin Diagn Pathol 15:85–101

Coffin CM, Patel A, Perkins S et al (2001) ALK1 and p80 expression and chromosomal rearrangements involving 2p23 in inflammatory myofibroblastic tumor. Mod Pathol 14:569–576

Coffin CM, Hornick JL, Fletcher CD (2007) Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol 31:509–520

Coindre JM, Chibon F (2010) Grading of soft tissue sarcomas – from histologic to molecular assessment. In: Companion meeting of the international society of bone and soft tissue pathology, Washington DC, March 2010 www.uscap.org

Coindre JM, Terrier P, Bui NB et al (1996) Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 14:869–877

Cole CH, Magee JF, Gianoulis M, Rogers PC (1993) Malignant fibrous histiocytoma in childhood. Cancer 71:4077–4083

Cook JR, Dehner LP, Collins MH et al (2001) Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor: a comparative immunohistochemical study. Am J Surg Pathol 25:1364–1371

Corpron CA, Black CT, Raney RB et al (1996) Malignant fibrous histiocytoma in children. J Pediatr Surg 31:1080–1083

Dal Cin P, Brock P, Casteels-Van Daele M et al (1991) Cytogenetic characterization of congenital or infantile fibrosarcoma. Eur J Pediatr 150:579–581

Dantonello T, Int-Veen C, Leuschner I et al (2008) Mesenchymal chondrosarcoma of soft tissues and bone in children, adolescents, and young adults: experiences of the CWS and COSS study groups. Cancer 112:2424–2431

De Saint Aubain Somerhausen N, Fletcher CDM (1999) Leiomyosarcoma of soft tissue in children: clinicopathologic analysis of 20 cases. Am J Surg Pathol 23:755–763

Denschlag D, Kontny U, Tempfer C et al (2005) Low-grade myxofibrosarcoma of the vulva in a 15-year-old adolescent: a case report. Int J Surg Pathol 13:117–119

Deyrup AT, Lee VK, Hill CE et al (2006) Epstein- Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol 30:75–82

Dômont J, Salas S, Lacroix L et al (2010) High frequency of beta-catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management. Br J Cancer 102:1032–1036

Eble JN, Amin MB, Young RH (1997) Epithelioid angiomyolipoma of the kidney: a report of five cases with a prominent and diagnostically confusing epithelioid smooth muscle component. Am J Surg Pathol 21:1123–1130

Eilber FC, Brennan MF, Eilber FR et al (2007) Chemotherapy is associated with improved survival in adult patients with primary extremity synovial sarcoma. Ann Surg 246:105–113

Enzinger FM (1965) Clear cell sarcoma of tendons and aponeuroses. An analysis of 21 cases. Cancer 18:1163–1174

Enzinger FM (1970) Epitheloid sarcoma. A sarcoma simulating a granuloma or a carcinoma. Cancer 26:1029–1041

Evans HL (1987) Low-grade fibromyxoid sarcoma. A report of two metastasizing neoplasms having a deceptively benign appearance. Am J Clin Pathol 88:615–619

Evans DGR, Baser ME, McGaughran J et al (2002) Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 39:311–314

Ferrari A (2008) Role of chemotherapy in pediatric nonrhabdomyosarcoma soft-tissue sarcomas. Expert Rev Anticancer Ther 8:929–938

Ferrari A (2009) Harmonizing adult and pediatric approaches to the treatment of soft tissue sarcoma. Expert Rev Anticancer Ther 9:1541–1543

Ferrari A, Casanova M (2005) New concepts for the treatment of pediatric non-rhabdomyosarcoma soft tissue sarcomas. Expert Rev Anticancer Ther 5:307–318

Ferrari A, Casanova M, Spreafico F et al (1999) Childhood liposarcoma: a single-institutional twenty-year experience. Pediatr Hematol Oncol 16:1–7

Ferrari A, Bisogno G, Casanova M et al (2001) Childhood leiomyosarcoma: a report from the Soft-tissue Sarcoma Italian Cooperative Group. Ann Oncol 12:1163–1168

Ferrari A, Casanova M, Bisogno G et al (2002) Clear cell sarcoma of tendons and aponeuroses in pediatric patients: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. Cancer 94:3269–3276

Ferrari A, Gronchi A, Casanova M et al (2004) Synovial sarcoma: a retrospective analysis of 271 patients of all ages treated at a single institution. Cancer 101:627–634

Ferrari A, Brecht IB, Koscielniak E et al (2005a) The role of adjuvant chemotherapy in surgically-resected adult-type soft tissue sarcomas of children and adolescents. Pediatr Blood Cancer 45:128–134

Ferrari A, Casanova M, Meazza C et al (2005b) Adult-type soft tissue sarcomas in pediatric age: experience at the Istituto Nazionale Tumori in Milan. J Clin Oncol 23:4021–4030

Ferrari A, Bisogno G, Macaluso A et al (2007a) Soft tissue sarcomas in children and adolescents with neurofibromatosis type 1. Cancer 109:1406–1412

Ferrari A, Miceli R, Casanova M et al (2007b) Adult-type soft tissue sarcomas in pediatric age: a nomogram-based prognostic comparison with adult sarcomas. Eur J Cancer 43:2691–2697

Ferrari A, Bisogno G, Alaggio G et al (2008) Synovial sarcoma of children and adolescents: the prognostic role of axial sites. Eur J Cancer 44:1202–1209

Ferrari A, Miceli R, Meazza C et al (2009) Soft tissue sarcomas of childhood and adolescence: the prognostic role of tumour size in relation to patient body size. J Clin Oncol 27: 371–376

Ferrari A, Miceli R, Rey A et al (2011) Non metastatic unresected pediatric non-rhabdomyosarcoma soft tissue sarcomas: results of a pooled analysis from United States and European groups. Eur J Cancer 47:724–731

Ferrari A, Sultan I, Rodriguez-Galindo C et al (2011) Soft tissue sarcoma across the age spectrum: a population-based study from the surveillance epidemiology and end results database. Pediatr Blood Cancer 57(6):943–949

Fetsch JF, Miettinen M, Laskin WB et al (2000) A clinicopathologic study of 45 pediatric soft tissue tumors with an admixture of adipose tissue and fibroblastic elements, and a proposal for classification as lipofibromatosis. Am J Surg Pathol 24: 1491–1500

Fetsch JF, Laskin WB, Miettinen M (2005) Palmar-plantar fibromatosis in children and preadolescents: a clinicopathologic study of 56 cases with newly recognized demographics and extended follow- up information. Am J Surg Pathol 29: 1095–1105

Fiore M, Rimareix F, Mariani L et al (2009) Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. Ann Surg Oncol 6:2587–2593

Fisher C (2004) Myofibrosarcoma. Virchows Arch 445:215–223

Fletcher CD (1992) Pleomorphic malignant fibrous histiocytoma: fact or fiction? A critical reappraisal based on 159 tumors diagnosed as pleomorphic sarcoma. Am J Surg Pathol 16:213–228

Folpe AL, Deyrup AT (2006) Alveolar soft-part sarcoma: a review and update. J Clin Pathol 59:1127–1132

Folpe AL, Goodman ZD, Ishak KG et al (2000a) Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. Am J Surg Pathol 24(9):1239–1246

Folpe AL, Lane KL, Paull G, Weiss SW (2000b) Low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with giant rosettes: a clinicopathologic study of 73 cases supporting their identity and assessing the impact of high-grade areas. Am J Surg Pathol 24:1353–1360

Frustaci S, Gherlinzoni F, De Paoli A et al (2001) Adjuvant chemotherapy for adult soft tissue sarcomas of extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol 19:1238–1247

Gleason BC, Hornick JL (2008) Inflammatory myofibroblastic tumours: where are we now? J Clin Pathol 61:428–437

Goodman ZD, Ishak KG (1984) Angiomyolipomas of the liver. Am J Surg Pathol 8:745–750

Gora-Gebka M, Liberek A, Bako W, Szumera M, Korzon M, Jaskiewicz K (2006) The "sugar" clear cell tumor of the lung-clinical presentation and diagnostic difficulties of an unusual lung tumor in youth. J Pediatr Surg 41(6):27–29

Greenspan A (1993) Benign bone-forming lesions: osteoma, osteoid osteoma, and osteoblastoma. Clinical, imaging, pathologic, and differential considerations. Skeletal Radiol 22:485

Gross E, Rao BN, Pappo A et al (1996) Epithelioid sarcoma in children. J Pediatr Surg 31:1663–1665

Grosso F, Jones RL, Demetri GD et al (2007) Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. Lancet Oncol 8:595–602

Guillou L, Coindre JM, Bonichon F et al (1997a) Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 15:350–362

Guillou L, Wadden C, Coindre JM et al (1997b) "Proximal-type" epithelioid sarcoma, a distinctive aggressive neoplasm showing rhabdoid features. Clinicopathologic, immunohistochemical, and ultrastructural study of a series. Am J Surg Pathol 21:130–146

Guillou L, Benhattar J, Bonichon F et al (2004) Histologic grade, but not SYT-SSX fusion type, is an important prognostic factor in patients with synovial sarcoma: a multicenter, retrospective analysis. J Clin Oncol 22:4040–4050

Guillou L, Benhattar J, Gengler C et al (2007) Translocation-positive low- grade fibromyxoid sarcoma: clinicopathologic and molecular analysis of a series expanding the morphologic spectrum and suggesting potential relationship to sclerosing epithelioid fibrosarcoma: a study from the French Sarcoma Group. Am J Surg Pathol 31:1387–1402

Hayes-Jordan AA, Spunt SL, Poquette CA et al (2000) Nonrhabdomyosarcoma soft tissue sarcomas in children: is age at diagnosis an important variable? J Pediatr Surg 35: 948–954

Heinrich MC, McArthur GA, Demetri GD et al (2006) Clinical and molecular studies of the effect of imatinib on advanced aggressive fibromatosis (desmoid tumor). J Clin Oncol 24: 1195–1203

Hensley ML, Maki R, Venkatraman E et al (2002) Gemcitabine and Docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 20:2824–2831

Hornick JL, Fletcher CD (2006) PEComa: what do we know so far? Histopathology 48(1):75–82

Hornick JL, Dal Cin P, Fletcher CD (2009) Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. Am J Surg Pathol 33:542–545

Hulbert JC, Graf R (1983) Involvement of the spleen by renal angiomyolipoma: metastasis or multicentricity? J Urol 130: 328–329

Hussong JW, Brown M, Perkins SL et al (1999) Comparison of DNA ploidy, histologic, and immunohistochemical findings with clinical outcome in inflammatory myofibroblastic tumors. Mod Pathol 12:279–286

Kavunkal AM, Pandiyan MS, Philip MA, Parimelazhagan KN, Manipadam MT, Cherian VK (2007) Large clear cell tumor of the lung mimicking malignant behavior. Ann Thorac Surg 83(1):310–312

Kawaguchi S, Wada T, Ida K et al (2005) Phase I vaccination trial of SYT-SSX junction peptide in patients with disseminated synovial sarcoma. J Transl Med 12:1

Kaweblum M, Lehman WB, Bash J et al (1993) Diagnosis of osteoid osteoma in the child. Orthop Rev 22:1305

Keller C, Gibbs CN, Kelly SM et al (2004) Low- grade myofibrosarcoma of the head and neck: importance of surgical therapy. J Pediatr Hematol Oncol 26:119–120

Kenerson H, Folpe AL, Takayama TK et al (2007) Activation of the mTOR pathway in sporadic angiomyolipomas and other epithelioid cell neoplasms. Hum Pathol 38:1361–1371

Kneisl JS, Simon MA (1992) Medical management compared with operative treatment for osteoid-osteoma. J Bone Joint Surg Am 74:179

Knezevich SR, Garnett MJ, Pysher TJ et al (1998) ETV6-NTRK3 gene fusions and trisomy 11 establish a histogenetic link between mesoblastic nephroma and congenital fibrosarcoma. Cancer Res 58:5046–5048

Kodet R, Newton WA, Sachs N et al (1991) Rhabdoid tumors of soft tissues: a clinicopathologic study of 26 cases enrolled on the Intergroup Rhabdomyosarcoma Study. Hum Pathol 22: 674–684

Kodet R, Smelhaus V, Newton WA et al (1994) Epithelioid sarcoma in childhood: an immunohistochemical, electron microscopic, and clinicopathologic study of 11 cases under 15 years of age and review of the literature. Pediatr Pathol 14: 433–451

Kushner BH, La Quaglia MP, Wollner N et al (1996) Desmoplastic small round-cell tumour: prolonged progression-free survival with aggressive multimodality therapy. J Clin Oncol 14:1526–1531

La Quaglia MP, Spiro SA, Ghavimi F et al (1993) Liposarcoma in patients younger than or equal to 22 years of age. Cancer 72:3114–3119

Ladanyi M, Lui MY, Antonescu CR et al (2001) The der(17) t(X;17)(p11;q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. Oncogene 20:48–57

Lane KL, Shannon RJ, Weiss SW (1997) Hyalinizing spindle cell tumor with giant rosettes: a distinctive tumor closely resembling low- grade fibromyxoid sarcoma. Am J Surg Pathol 21:1481–1488

Lazar AJ, Tuvin D, Hajibashi S et al (2008) Specific mutations in the beta- catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol 173:1518–1527

Lazar AJ, Lahat G, Myers SE et al (2009) Validation of potential therapeutic targets in alveolar soft part sarcoma: an immunohistochemical study utilizing tissue microarray. Histopathology 55:750–755

Lewis JJ, Antonescu CR, Leung DH et al (2000) Synovial sarcoma: a multivariate analysis of prognostic factors in 112 patients with primary localized tumours of the extremity. J Clin Oncol 18:2087–2094

Liu J, Hudkins PG, Swee RG, Unni KK (1987) Bone sarcomas associated with Ollier's disease. Cancer 59:1376

Mai KT, Perkins DG, Collins JP (1996) Epithelioid cell variant of renal angiomyolipoma. Histopathology 28:277–280

Maki R, Wathen JK, Patel SR et al (2007) Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of Sarcoma Alliance for Research Through Collaboration study 002. J Clin Oncol 5:2755–2763

Mancuso T, Mezzekani A, Riva C et al (2000) Analysis of SYT-SSX fusion transcripts and bcl-2 expression phosphorylation status in synovial sarcoma. Lab Invest 80:805–813

Mandahl N, Heim S, Rydholm A et al (1989) Nonrandom numerical chromosome aberrations (+8, +11, +17, +20) in infantile fibrosarcoma. Cancer Genet Cytogenet 40:137–139

Martignoni G, Pea M, Bonetti F et al (1998) Carcinoma-like monotypic epithelioid angiomyolipoma in patients without evidence of tuberous sclerosis: a clinicopathologic and genetic study. Am J Surg Pathol 22:663–672

Martignoni G, Pea M, Reghellin D, Zamboni G, Bonetti F (2007) Perivascular epithelioid cell tumor (PEComa) in the genitourinary tract. Adv Anat Pathol 14(1):36–41

Martignoni G, Pea M, Reghellin D, Zamboni G, Bonetti F (2008) PEComas: the past, the present and the future. Virchows Arch 452(2):119–132

Matsui K, Tatsuguchi A, Valencia J et al (2000) Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. Hum Pathol 31:1242–1248

McArthur GA, Demetri GD, van Oosterom A et al (2003) Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225. J Clin Oncol 23:866–873

Meazza C, Bisogno G, Gronchi A et al (2010) Aggressive fibromatosis in children and adolescents: the Italian experience. Cancer 116:233–240

Meis-Kindblom JM, Kindblom LG, Enzinger FM (1995) Sclerosing epithelioid fibrosarcoma. A variant of fibrosarcoma simulating carcinoma. Am J Surg Pathol 19:979–993

Mertens F, Fletcher CD, Antonescu CR et al (2005) Clinicopathologic and molecular genetic characterization of low-grade fibromyxoid sarcoma, and cloning of a novel FUS/CREB3L1 fusion gene. Lab Invest 85:408–415

Mezzelani A, Mariani L, Tamborini E et al (2001) SYT-SSX fusion genes and prognosis in synovial sarcoma. Br J Cancer 85:1535–1539

Mirra JM, Kessler S, Bhuta S, Eckardt J (1992) The fibroma-like variant of epithelioid sarcoma. A fibrohistiocytic/myoid cell lesion often confused with benign and malignant spindle cell tumors. Cancer 69:1382–1395

Mita MM, Britten CD, Poplin E et al (2008) Deferolimus trial 106 – a phase I trial evaluating 7 regimens of oral deferolimus (AP23573, MK-8669). J Clin Oncol 26:15S (Abstract 3509)

Montgomery E, Goldblum JR, Fisher C (2001) Myofibrosarcoma: a clinicopathologic study. Am J Surg Pathol 25:219–228

Mueller BU, Butler KM, Higham MC et al (1992) Smooth muscle tumors in children with human immunodeficiency virus infection. Pediatrics 90:460–463

Nagy B, Nábrády Z, Nemes Z (1998) Pulmonary lymphangiomyomatosis in a preadolescent girl. N Engl J Med 338(7):473–474

Nehra D, Vagefi PA, Chang H, Louissaint A, Mino-Kenudson M et al (2010) Clear cell sugar tumor of the lung masquerading as tuberculosis in a pediatric patient. J Thorac Cardiovasc Surg 139(5):e108–e109

Okcu MF, Munsell M, Treuner J et al (2003) Synovial sarcoma of childhood and adolescence: a multicenter, multivariate analysis of outcome. J Clin Oncol 21:1602–1611

Orbach D, Rey A, Cecchetto G et al (2010) Infantile fibrosarcoma: place of chemotherapy and treatment proposals based on the European experience. J Clin Oncol 28:318–323

Pan CC, Jong YJ, Chai CY et al (2006) Comparative genomic hybridization study of perivascular epithelioid cell tumor: molecular genetic evidence of perivascular epithelioid cell tumor as a distinctive neoplasm. Hum Pathol 37(5): 606–612

Pan CC, Chung MY, Ng KF, Liu CY et al (2008) Constant allelic alteration on chromosome 16p (TSC2 gene) in perivascular epithelioid cell tumour (PEComa): genetic evidence for the relationship of PEComa with angiomyolipoma. J Pathol 214(3):387–393

Pappo AS, Devidas M, Jenkins J et al (2005) Phase II trial of neoadjuvant vincristine, ifosfamide, and doxorubicin with granulocyte colony-stimulating factor support in children and adolescents with advanced-stage nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. J Clin Oncol 23:4031–4038

Parham DM, Weeks DA, Beckwith JB (1994) The clinicopathologic spectrum of putative extrarenal rhabdoid tumors. An analysis of 42 cases studied with immunohistochemistry or electron microscopy. Am J Surg Pathol 18:1010–1029

Parham DM, Webber BL, Jenkins JJ et al (1995) Nonrahbdomyosarcomatous soft tissue sarcomas of childhood: formulation of a simplified system for grading. Mod Pathol 8:705–710

Patel S, Pappo A, Crowley J et al (2010) A SARC global collaborative phase II trial of R1507, a recombinant human monoclonal antibody to the insulin-like growth factor-1 receptor (IGF1R) in patients with recurrent or refractory sarcomas. J Clin Oncol 27:15S (Abstract 10503)

Pea M, Bonetti F, Zamboni G et al (1991) Melanocyte-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney. Pathology 23:185–188

Peh SC, Sivanesaratnam V (1988) Angiomyolipoma of the vagina–an uncommon tumour. Case report. Br J Obstet Gynaecol 95:820–823

Penel N, Bui B, Bay JO et al (2008) Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol 26:5269–5274

Pratt CB, Pappo AS, Gieser P et al (1999) Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. J Clin Oncol 17:1219–1226

Qureshi AA, Shott S, Mallin BA, Gitelis S (2000) Current trends in the management of adamantinoma of long bones. An international study. J Bone Joint Surg Am 82:1122

Salas S, Chibon F, Noguchi T et al (2010) Molecular characterization by array comparative genomic hybridization and DNA sequencing of 194 desmoid tumours. Genes Chromosomes Cancer 49:560–568

Santoro A, Tursz T, Mouridsen H et al (1995) Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 13:1537–1545

Sarcoma Meta-analysis Collaboration (1997) Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 350:1647–1654

Schoffski P, Ray-Coquard IL, Cioffi A et al (2010) Activity of eribulin mesylate (E7389) in patients with soft tissue sarcoma (STS): phase II studies of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC 62052). J Clin Oncol 28:15S (Abstract 10031)

Schofield DE, Beckwith JB, Sklar J (1996) Loss of heterozygosity at chromosome regions 22q11-12 and 11p15.5 in renal rhabdoid tumors. Genes Chromosomes Cancer 15:10–17

Shmookler BM, Enzinger FM (1983) Liposarcoma occurring in children. An analysis of 17 cases and review of the literature. Cancer 52:567–574

Silve C, Juppner H (2006) Ollier disease. Orphanet J Rare Dis 1:37

Skapek SX, Ferguson WS, Granowetter L et al (2007) Vinblastine and methotrexate for desmoid fibromatosis in children: results of a Pediatric Oncology Group Phase II Trial. J Clin Oncol 25:501–506

Sleijfer S, Ray-Coquard I, Papai Z et al (2009) Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 27:3126–3132

Smith DM, Mahmoud HH, Jenkins JJ et al (1995) Myofibrosarcoma of the head and neck in children. Pediatr Pathol Lab Med 15:403–418

Spunt SL, Poquette CA, Hurt YS et al (1999) Prognostic factors for children and adolescents with surgically resected nonrhabdomyosarcoma soft tissue sarcoma: an analysis of 121 patients treated at St Jude Children's Research Hospital. J Clin Oncol 17:3697–3705

Spunt SL, Ashley Hill D, Motosue AM et al (2002) Clinical features and outcome of initially unresected nonmetastatic pediatric nonrhaddomyosarcoma soft tissue sarcoma. J Clin Oncol 20:3225–3235

Subbiah V, Trent JC, Kurzrock R (2010) Resistance to mammalian target of rapamycin inhibitor therapy in perivascular epithelioid cell tumors. J Clin Oncol 28(24):415

Sultan I, Rodriguez-Galindo C, Saab R et al (2009) Comparing children and adults with synovial sarcoma in the Surveillance, Epidemiology and End Results Program, 1983 to 2005: an analysis of 1268 patients. Cancer 115:3537–3547

Tamborini E, Bonadiman L, Greco A et al (2004) Expression of ligand-activated KIT and platelet-derived growth factor receptor β tyrosine kinase receptors in synovial sarcoma. Clin Cancer Res 10:938–943

Tanaka M, Kato K, Gomi K et al (2009) Perivascular epithelioid cell tumor with SFPQ/PSF-TFE3 gene fusion in a patient with advanced neuroblastoma. Am J Surg Pathol 33(9):1416–1429

Thomas D, Skubitz T (2009) Giant cell tumour of bone. Curr Opin Oncol 21:338–344

Thomas DG, Giordano TJ, Sanders D et al (2005) Expression of receptor tyrosine kinases growth factor receptor and HER-2/neu in synovial sarcoma. Cancer 103:830–838

Thomas D, Henshaw R, Skubitz K et al (2010) Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol 11:275–280

Torres VE, Bjornsson J, King BF et al (1995) Extrapulmonary lymphangioleiomyomatosis and lymphangiomatous cysts in tuberous sclerosis complex. Mayo Clin Proc 70:641–648

Trassard M, Le Doussal V, Hacene K et al (2001) Prognostic factors in localized primary synovial sarcoma: a multicenter study of 128 adult patients. J Clin Oncol 19:525–534

Tsuda M, Davis IJ, Argani P et al (2007) TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res 67:919–929

Urban M, Feldberg L, Janssen A, Elliot D (1996) Dupuytren's disease in children. J Hand Surg Br 21:112–116

van Echten J, van den Berg E, van Baarlen J et al (1995) An important role for chromosome 17, band q25, in the histogenesis of alveolar soft part sarcoma. Cancer Genet Cytogenet 82:57–61

Van Rijn R, Bras J, Schaap G et al (2006) Adamantinoma in childhood: report of six cases and review of the literature. Pediatr Radiol 36:1068–1074

Versteege I, Sevenet N, Lange J et al (1998) Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature 394:203–206

Vijayabhaskar R, Mehta SS, Deodhar KK, Pramesh CS, Mistry RC (2010) PEComa of the lung. J Cancer Res Ther 6(1): 109–111

von Hochstetter AR, Meyer VE, Grant JW et al (1991) Epithelioid sarcoma mimicking angiosarcoma: the value of immunohistochemistry in the differential diagnosis. Virchows Arch A Pathol Anat Histopathol 418:271–278

Wagner AJ, Malinowska-Kolodziej I, Morgan JA et al (2010) Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol 28: 835–840

Watanabe K, Suzuki T (1999) Mucocutaneous angiomyolipoma. A report of 2 cases arising in the nasal cavity. Arch Pathol Lab Med 123:789–792

Weeks DA, Beckwith JB, Mierau GW (1989) Rhabdoid tumor. An entity or a phenotype? Arch Pathol Lab Med 113: 113–114

Weinreb I, Howarth D, Latta E et al (2007) Perivascular epithelioid cell neoplasms (PEComas): four malignant cases expanding the histopathological spectrum and a description of a unique finding. Virchows Arch 450(4):463–470

WHO Classification of Tumours (2002) Pathology and Genetics. Tumours of Soft Tissue and Bone. CDM Fletcher, KK Unni, and F Mertens eds. IARC Press, Lyon

Wick MR, Ritter JH, Dehner LP (1995) Malignant rhabdoid tumors: a clinicopathologic review and conceptual discussion. Semin Diagn Pathol 12:233–248

Wyers MR (2010) Evaluation of pediatric bone lesions. Pediatr Radiol 40:468

Yildiz C, Erler K, Atesalp AS, Basbozkur M (2003) Benign bone tumors in children. Curr Opin Pediatr 15:58

Zamboni G, Pea M, Martignoni G, Zancanaro C et al (1996) Clear cell "sugar" tumor of the pancreas. A novel member of the family of lesions characterized by the presence of perivascular epithelioid cells. Am J Surg Pathol 20:722–730

Part XII

Tumors of Unknown Primary Site

Tumors of Unknown Primary

45

Thomas A. Olson

Contents

45.1 Cancers of Unknown Origin: Adult Patients

The primary site of a metastatic carcinoma is not identified in approximately 3% of patients. It has been called a CUP or occult primary malignancy (Briasoulis and Pavlidis 1997; Pavlidis 2003; Pavlidis et al. 2003). In adult patients, distribution does not match usual distribution patterns. The most common tumors that present as CUPs are carcinoma of the lung and pancreas. Common malignancies such as colorectal, breast and prostate cancer are infrequently first identified as a CUP (Neumann and Nystrom 1982; Altman and Cadman 1986). The pattern of spread can usually aid in the diagnosis of a CUP. However, the pattern may differ significantly from the known primary of a similar carcinoma. The biological basis for this is unknown (Neumann and Nystrom 1982). Although few patients will have curable disease at diagnosis, it is important to employ modern imaging techniques coupled with molecular studies to identify those patients who may have a response.

45.2 Cancers of Unknown Origin: Pediatric Patients

There are few reports of malignancy of unknown primaries in children. In a retrospective review of the St. Jude's experience (over 30 years), Kuttesch et al. (1995) reported on 17 patients with embryonal malignancies without an identifiable primary in children. These patients had originally been identified as CUP. After extensive studies, a primary site was identified in only five patients. Two primary sites were identified during treatment. Three were identified at autopsy. The

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Table 45.1 Diagnostic strategy for CUP in pediatrics

Thorough medical history and physical examination with attention to sites of adenocarcinoma in adults (breast, head and neck, rectum) and in particular to nodal areas
Basic laboratory tests including CBC, chemistries, UA, and test for occult blood in stools. Laboratory tests that may be specific for certain tumors
Scans should be directed to suspected primary sites (CT chest/abdomen/pelvis). CT/FDG-PET may be beneficial
Specific areas to be assessed according to locations of involved nodes
Specific immunochemistry
Collection of material for molecular studies
Consideration of possible resource centers outside of organization

survival was poor (median 6 months), but three patients were long term survivors. Most patients had either rhabdomyosarcoma or neuroblastoma. The authors concluded that extensive search for the primary tumor was not indicated as long as adequate sampling could confirm the histology. This becomes more relevant in the molecular biology age. Consider, the Midline carcinoma with NUTT gene re-arrangement (French et al. 2004). Previously, patients were subjected to extensive studies and often repeat biopsies. Now that this entity has been identified by molecular biology techniques, perhaps a treatment solution can be obtained through further molecular studies.

45.3 Diagnostic Staging

Most strategies for staging must be gleaned from the adult oncology literature. In adult oncology, there is serious debate on the value of extensive evaluations to determine the primary in these patients. The most important strategy for diagnostic staging starts with a complete medical history and through physical examination (Briasoulis et al. 2009). Other basic investigations are listed in Table 45.1. There are some presentations that might be gender or location specific. One example would be prostate cancer that is amenable to hormone treatment. A prostate-specific antigen (PSA) might be helpful. Obviously, in both adult and pediatric oncology, the identification of curable metastatic diseases should be pursued. Two examples, in both pediatric and adult oncology, are germ cell tumors and lymphomas. Primitive midline germ cell tumors may be identified by measuring alpha-fetoprotein (AFP) and human chorionic gonadotropin (B-HCG) levels. In adolescents and adults, isochromosome 12p can also help establish the diagnosis of germ cell tumor (Bosl et al. 1994). For the majority of CUPs, one can question the cost/benefit ratio of extensive diagnostic studies (Maisey and Ellam 1984; Schapira and Jarrett 1995). FDG-PET might provide more direction for the discovery of unknown primaries. Bohuslavizki et al. reported on 53 adult patients with tumors metastatic to lymph nodes without a known primary (Bohuslavizki et al. 2000). FDG PET detected lesions in 27/53 patients. One patient declined further studies and in 6/27 patients the FDG PET was a false-positive. However, in 20/27, FDG PET did identify the lesion. In several patients, the FDG PET confirmed a suspected lesion in breast and ileo-colonic area, where physicians anticipated finding the primary. FDG PET was useful for unusual sites in head and neck. They concluded that FDG PET might aid in search for CUP by identifying potential biopsy sites. There are no data on the application of FDG PET to identify tumors of unknown primary site in pediatric patients. Imaging should target areas that are suspected, given that most metastatic spread in carcinomas is nodal. Though this may not be true in pediatric embryonal cancers, strategies based on nodal location are described in Table 45.2. Axillary nodes, in women, should suggest the breast as a potential source of an adenocarcinoma. The presence of cervical adenopathy should lead to a thorough investigation of the head and neck. Two other presentations should be mentioned. Peritoneal carcinomatosis is most often associated with ovarian epithelial tumors (Strnad et al. 1989). Germ cell tumors and other childhood embryonal tumors may also present in this way. When multiple organs are involved, histological identification is paramount and an extensive search for a primary site may not be warranted. Many metastatic pediatric embryonal tumors may respond to chemotherapy. In the case of metastatic in front of germ cell. It si essential. germ cell tumor, cure may be achieved with chemotherapy.

45.4 Pathology: Cellular Classification

This book has been dedicated to the identification and treatment of rare pediatric tumors. The involvement of oncologists, surgeons, radiologists and pathologists

Table 45.2 Nodal metastases

Nodal location	Possible primaries	Diagnostics
Cervical	Head/neck, salivary, thyroid, lymphoma	CT/MRI head and neck, PET, guided biopsies
Axillary (isolated)	Breast, sarcomas of upper extremity, chest wall tumors, and lymphoma	Mammogram/breast MRI, chest CT, MRI of upper extremity
Supraclavicular	Lymphomas, spread from abdominal lymphomas, carcinomas, and germ cell tumors	CT chest and abdomen, PET
Inguinal	Lymphoma, testicular tumors, and sarcomas of extremities	Careful examination of extremity, MRI extremity, testicular ultrasound
Retroperitoneal	Embryonal small, blue cell tumors (neuroblastoma; rhabdomyosarcoma, lymphoma and primitive neuroectodermal tumors), small colonic carcinomas	CT/MRI of abdomen, PET
Isolated node	Melanoma	Careful examination

Table 45.3 Cellular classification – pediatric tumors

Method	Specifics	Diagnoses
Immunohistochemical	Keratins, myogen, desmin, S-100, AFP, B-HCG	Epithelial tumors, rhabdomyosarcoma, melanoma, Ewing's sarcoma
Cytogenetics	Translocations EWS variety, PAX 3	Ewing's sarcoma, alveolar rhabdomyosarcoma
Fish analysis	Similar targets as above but may applicable to paraffin block material	Ewing's sarcoma, alveolar rhabdomyosarcoma
PCR	EBV, i(12p)	NPC, germ cell tumors

with interest in rare pediatric cancers is most important in tumors of unknown primaries. The pathologist has a central role in the evaluation of CUPs. As stated above, collaboration with oncologists, surgeons and radiologists is essential. In addition, the pathologist must be keenly aware of the difficulties that these very primitive poorly differentiated tumors present. They must distinguish tumors of epithelial, hematopoietic or neuroectodermal origin. Cases of CUP in adults are broadly characterized by pathologists into several broad categories:

- Adenocarcinoma – well and moderately differentiated
- Adenocarcinoma – poorly differentiated
- Carcinomas – poorly differentiated
- Carcinomas with neuroendocrine features
- Squamous cell carcinomas
- Undifferentiated tumors, not otherwise specified

Immunochemistry is essential to help identify potential tumors, such as lymphoma, that may be chemosensitive (Pavlidis et al. 2010; Pavlidis and Pentheroudakis 2010). Immunostains for prostate-specific antigen (PSA) in males and estrogen and progesterone receptors (in women with axillary metastases) are advisable. In general, the ease of pathologic identification is inversely related to the degree of differentiation. Distinguishing germ cell tumors, sarcomas, or lymphomas from epithelial tumors may be easy if the tumors are well differentiated. However, if the tumor is very primitive and undifferentiated, identification may be very difficult. Some strategies to improve identification are described in Tables 45.3 and 45.4. It is crucial that both the surgeon and pathologist are in communication before the procedure, so that appropriate material can be obtained. The identification of embryonal pediatric tumors requires immunohistochemical studies and cytogenetics Table 45.3. The identification of many specific translocations and tumor fusion genes has significantly improved our ability to discover tumor origin sites in embryonal tumors. Immunohistochemical studies and applications of newer molecular methods have been applied to the identification of carcinoma primary sites (Table 45.4). Gene profiling has recently been

Table 45.4 Cellular classification – adult tumors

Site	Immunohistochemical	Molecular
Breast	Cytokeratins, ER, CK7+/CK20–	Gene expression profiling[a]
Colon	CEA, CK7–/CK20+	Gene expression profiling[a]
Lung	CK7+/CK20–	Ewing's sarcoma, alveolar rhabdomyosarcoma
Sarcoma	Vimentin, desmin	Specific translocations

[a]Horlings et al. (2008); Varadhachary et al. (2008); Varadhachary and Rabe (2009)

used to identify the tissue of origin for CUP. A molecular assay was developed that evaluated the expression of ten tissue-type-specific genemarkers using reverse-transcriptase PCR (RT-PCR). Six specific sites – lung, breast, colon, ovary, pancreas, and prostate – were targeted (Talantov et al. 2006). Using this technology and material from formalin-fixed paraffin-embedded (FFPE) specimens, the issue of origin was identified in 61% of CUP (Varadhachary et al. 2008). Gene expression profiling has also been used to successfully identify the site of origin of adenocarcinomas using FFPE (Horlings et al. 2008).This retrospective study was done in adult cancers and may not be applicable to pediatric cancers. But the methodology holds possibilities for the study of rare pediatric tumor. These specific studies have been developed at several research centers and are not commercially available. It must be emphasized that the cost-effectiveness of newer molecular studies, such as gene profiling, has not been determined (Varadhachary and Rabe 2009). However, it is critical that investigators continue these investigations, not only to help identify CUP, but to eventually develop treatment strategies.

45.5 Treatment Strategy

The key strategy must be the administration of tumor specific therapy. First, the cell of origin must be identified. Many advances have been made in pediatric embryonal tumors. However, the site of primary may significantly impact the treatment plan. Radiation is often essential for the successful treatment of solid tumors. Therefore, all tumor sites should be confirmed. However, in some cases, overall survival may be affected by the lack of information on primary site. One potential strategy, in this situation, might be a comprehensive surveillance program. It may be that the primary site may be identified later in the course of treatment, so an aggressive treatment approach to local control can be developed. Pediatric oncologists often have a different approach to "curability" because their patients have more embryonal tumors with a good prognosis. Strategies for confirmed histologies are suggested in Fig. 45.1. Embryonal pediatric tumors may be responsive to standard chemotherapy. This is especially true when histology has been confirmed. In rhabdomy-

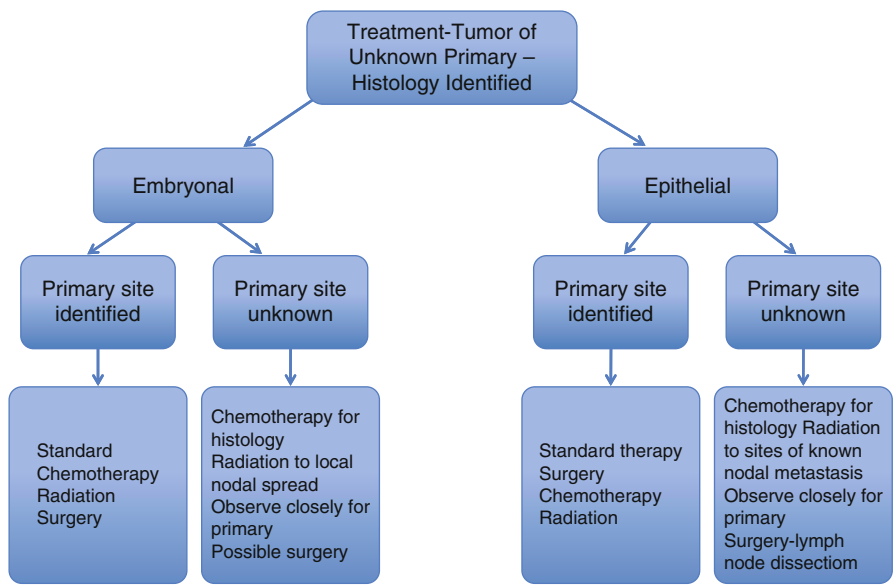

Fig. 45.1 Strategy for Treatment of Tumors of Unknown Origin with Known Histology

Table 45.5 Treatment of adult CUP malignancies

Cervial adenopathy – squamous cell carcinoma	Radical neck dissection +/– radiation therapy with platinum based chemotherapy for more advanced disease
Peritoneal serous adenocarcinoma in female	Treat as ovarian cancer with platinum +/– paclitaxel, response rates may approach ovarian treatment rates
Axillary adenopathy in female	Treat as node-positive breast cancer
Bone metastases and elevated PSA	Treat as prostate cancer – hormonal therapy
Adenocarcinoma – multiple metastatic sites	Palliation
Poorly differentiated carcinomas (+/– AFP, BHCG)	May be treated as primitive germ-cell tumors with BEP. Response rate near 60%
Poorly differentiated neuroendocrine tumors	Cisplatin/Doxorubicin combinations
Melanoma	Radical nodal dissection may yield survival better than in conventional stage II

osarcoma, this might preclude radiation to the primary site, resulting in relapse. The child with an adult epithelial tumor presents a different challenge. Gene-profiling has helped classify adult CUP. However, CUPs in adult patients may not respond as a similar tumor of known primary. Though histologically similar, these same tumors in pediatric patients, may have significantly different biologic characteristics and clinical behavior. Treatment options for unknown histology and unknown primary site are suboptimal at best. Most of these tumors are very primitive and palliation may be the only option. Several guidelines have been published recently for treatment of CUP in adults (Table 45.5) (Briasoulis et al. 2009; Pavlidis and Fizazi 2009; MacReady 2010; Pavlidis et al. 2010). It should be emphasized that these strategies are based on data from tumors that have an identified primary and histology.

References

Altman E, Cadman E (1986) An analysis of 1539 patients with cancer of unknown primary site. Cancer 57(1):120–124

Bohuslavizki KH, Klutmann S et al (2000) FDG PET detection of unknown primary tumors. J Nucl Med 41(5):816–822

Bosl GJ, Ilson DH et al (1994) Clinical relevance of the i(12p) marker chromosome in germ cell tumors. J Natl Cancer Inst 86(5):349–355

Briasoulis E, Pavlidis N (1997) Cancer of unknown primary origin. Oncologist 2(3):142–152

Briasoulis E, Pavlidis N et al (2009) Cancers of unknown primary site: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20(Suppl 4): 154–155

French CA, Kutok JL et al (2004) Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol 22(20):4135–4139

Horlings HM, van Laar RK et al (2008) Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. J Clin Oncol 26(27):4435–4441

Kuttesch JF Jr, Parham DM et al (1995) Embryonal malignancies of unknown primary origin in children. Cancer 75(1): 115–121

MacReady N (2010) NICE issues guidance on cancer of unknown primary. Lancet Oncol 11(9):824

Maisey MN, Ellam SV (1984) Investigating the adenocarcinoma of unknown origin (ACUP): a cost benefit analysis. Rev Epidemiol Sante Publique 32(1):57–61

Neumann KH, Nystrom JS (1982) Metastatic cancer of unknown origin: nonsquamous cell type. Semin Oncol 9(4): 427–434

Pavlidis N (2003) Cancer of unknown primary: biological and clinical characteristics. Ann Oncol 14(Suppl 3):iii11–iii18

Pavlidis N, Fizazi K (2009) Carcinoma of unknown primary (CUP). Crit Rev Oncol Hematol 69(3):271–278

Pavlidis N, Pentheroudakis G (2010) Cancer of unknown primary site: 20 questions to be answered. Ann Oncol 21(Suppl 7):vii303–vii307

Pavlidis N, Briasoulis E et al (2003) Diagnostic and therapeutic management of cancer of an unknown primary. Eur J Cancer 39(14):1990–2005

Pavlidis N, Hansen H et al (2010) ESMO clinical practice guidelines: development, implementation and dissemination. Ann Oncol 21(Suppl 5):v7–v8

Schapira DV, Jarrett AR (1995) The need to consider survival, outcome, and expense when evaluating and treating patients with unknown primary carcinoma. Arch Intern Med 155(19): 2050–2054

Strnad CM, Grosh WW et al (1989) Peritoneal carcinomatosis of unknown primary site in women. A distinctive subset of adenocarcinoma. Ann Intern Med 111(3):213–217

Talantov D, Baden J et al (2006) A quantitative reverse transcriptase-polymerase chain reaction assay to identify metastatic carcinoma tissue of origin. J Mol Diagn 8(3): 320–329

Varadhachary GR, Rabe MN (2009) Gene expression profiling in cancers of unknown primary. J Clin Oncol 27(25):e85–e86, author reply e87–88

Varadhachary GR, Talantov D et al (2008) Molecular profiling of carcinoma of unknown primary and correlation with clinical evaluation. J Clin Oncol 26(27):4442–4448

Part XIII

Rare Tumors as Second Malignancies

Rare Subsequent Primary Cancers in Pediatric Cancer Survivors

46

Ann C. Mertens and Thorsten Langer

Contents

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46.1 Introduction

Advances in cancer therapy during the past four decades have resulted in remarkable increases in survival for most cancers of childhood and adolescence. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program show that the overall 5-year survival rate for childhood cancer has increased from 45% in 1970 to over 80% in 2005 (Ries et al. 1999). It is estimated that one in every 640 young adults is now a survivor of childhood cancer, and that at least 328,000 persons in the USA alone have survived cancer diagnosed before the age of 20 years (Mariotto et al. 2009). Because of the relatively young age of these survivors, and their potential longevity, the delayed consequences of therapy may have a significant impact on their lives, and on society at large, over an extended period of time.

Also with this success has come the realization that a substantial proportion of childhood cancer survivors will experience late-occurring adverse health effects resulting from their disease and treatment. As pediatric cancer survivors are being followed long-term, nearly 73% of adult survivors of pediatric cancer have chronic health conditions, many of which are severe or disabling (Oeffinger et al. 2006). Numerous reports and reviews of late effects of chemotherapy and radiation have been published, describing sequelae present at, or shortly following, the end of therapy, as well as the occurrence of selected late complications. Most studies of late sequelae have focused on medical outcomes (Oeffinger and Hudson 2004). These studies have shown that the type and intensity of therapy, as well as the age at therapy, are important factors in both overall survival as well as late effects outcomes. Children who

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are younger at diagnosis and treatment are more severely affected than older children, particularly if treatment is administered at a significant time of development and growth.

One of the most devastating late effects is the development of a subsequent primary cancer that originates in a new primary site or tissue. Over the past 30 years, numerous reports and reviews of late effects of chemotherapy and radiation have been published, describing an increased risk of developing subsequent malignant neoplasms in survivors of childhood cancers. The incidence of subsequent primary cancers has been primarily linked to treatment, which is demonstrated in higher rates in certain types of cancer who receive these multimodal treatments (Ng et al. 2010). Other primary subsequent cancer has been linked to genetic predisposition to multiple cancers and sensitivity to radiogenic cancer, which has been demonstrated in children diagnosed with retinoblastoma (Kleinerman et al. 2005).

46.2 Study Findings

Information we have on the development of rare subsequent cancer in pediatric cancer survivors comes from two major sources: reports from the Surveillance, Epidemiology, and End Results (SEER) Program; and three large studies that have followed pediatric cancer survivors into adulthood. From these studies, it is clear that the major types of subsequent cancers are due to radiation exposure and certain chemotherapies, particularly alkylating agents. Recent studies have also indicated that the incidence of basal cell carcinoma is also very high in the survivor population. However, this is more difficult to enumerate since there are no record keeping of these cancers in the general population. The more rare cancers in this pediatric cancer survivor population are described below.

46.2.1 Surveillance, Epidemiology, and End Results (SEER) Program

SEER data is a compilation of population-based registries allowing for objective assessments and now covers 26% of the US population. In a recent monograph published through SEER looking at New Malignancies Among Cancer Survivors, descriptive analysis on new malignancies following childhood cancer was highlighted (Curtis et al. 2006). This study population included 23,819 children diagnosed with cancer before the age of 18, who had survived 2 or more months following diagnosis. This population was observed for an average of 8.3 years (median, 5.8 years). Within this population, there were 12,951 5-year survivors, 8,424 10-year survivors, and 2,637 20-year survivors. The maximum age at the end of follow-up was 44 years.

During this follow-up period, 352 new primary cancers were diagnosed in 327 individuals, accounting for a sixfold increase in incidence relative to the general population (observed/expected (O/E) = 6.07, 95% CI = 5.45–6.74, excess absolute risk (EAR) = 15 per 10,000 person-years). Of particular concern in this cohort is the occurrence of new primary cancers in this young population of longer-term survivors. The pattern of cancer incidence in this group patterned the cancer incidence seen more commonly in older adults. The more rare but significant subsequent primary cancers were diagnosed in the buccal cavity, digestive, respiratory, male genital, urinary, and central nervous system. Within these systems, increased risk of subsequent primary cancers due to radiation exposure were noted in cancers found in the salivary gland (O/E = 27.13), stomach (O/E = 35.89), pancreas (O/E = 69.36), and lung (O/E = 14.20).

In addition, childhood cancer patients whose initial treatment included radiotherapy were at higher risk of developing a subsequent cancer than those not given radiotherapy, as reflected by the high O/E ratios and absolute risks seen (Table 46.1). Subsequent cancer sites showing the greatest increased risk following radiotherapy among 5-year survivors included breast, brain, bone and soft tissue, thyroid gland, digestive system, and lung. Also of interest is the increased risk of melanoma and the female and male genital system in patients without radiotherapy.

46.2.2 Population-Based Studies

In the synopsis of current data on subsequent primary cancers, two large population-based studies are highlighted due to the long average follow-up period of pediatric cancer survivors into adulthood. Both studies, using age-, sex-, and calendar time-specific comparisons with the general population, demonstrate that the risk of a subsequent cancer is substantially higher than that seen in the general population.

Table 46.1 Risk of subsequent primary cancers following childhood cancer by initial treatment with radiation

	Any radiation ($n=9,063$)				No radiation ($n=13,905$)			
Subsequent primary cancer	Observed	Expected	O/E	EAR	Observed	Expected	O/E	EAR
Buccal cavity, pharynx	7	0.47	15.03*	0.80	10	0.55	18.25*	0.87
Salivary gland	4	0.15	27.13*	0.47	4	0.18	22.03*	0.35
Digestive system	14	1.08	12.99*	1.59	10	1.29	7.74*	0.80
Stomach	4	0.11	35.89*	0.48	2	0.13	15.24*	0.17
Pancreas	5	0.07	69.36*	0.61	0	0.08	0.00	−0.01
Respiratory system	6	0.48	12.38*	0.68	2	0.57	3.48	0.13
Lung, bronchus	4	0.28	14.20*	0.46	1	0.32	30.9	0.06
Female breast	29	1.71	16.91*	7.14	10	2.08	4.81	1.48
Female genital system	3	2.14	1.40	0.22	7	2.56	2.73*	0.83
Male genital system	2	2.15	0.93	−0.03	10	2.24	4.46*	1.41
Urinary system	2	0.64	3.12	0.17	3	0.87	3.44	0.20
Melanoma of the skin	6	2.57	2.34	0.42	19	2.82	6.74	1.49
Brain, CNS	27	2.19	12.32*	30.5	12	3.00	4.00*	0.83
Thyroid	17	20.8	8.18*	1.83	12	2.41	4.99*	0.89
Bone, joints	23	0.80	28.83*	2.73	12	0.99	12.07*	1.02
Soft tissue	19	0.81	23.48*	2.23	7	1.09	6.45*	0.55
Hodgkin lymphoma	3	2.51	1.20	0.06	1	2.85	0.35	−0.17
Non-Hodgkin lymphoma	9	1.81	4.97*	0.88	6	2.11	2.85*	0.36
Acute lymphocytic leukemia	5	1.30	3.85*	0.45	3	2.09	1.44	0.08
Acute nonlymphocytic leukemia	12	0.72	16.66*	1.39	14	0.94	14.93*	1.21

O observed number of subsequent primary cancers, *E* expected number of subsequent primary cancers, *EAR* excess absolute risk (excess cancers per 10,000 person-years)
* $p<0.05$

Table 46.2 Risk of subsequent malignant neoplasms (SMN) after nonretinoblastoma childhood cancer by duration of follow-up from original diagnosis

	Follow-up period from diagnosis (years)			
	3–9	10–19	20–29	30 or more
Number of persons at risk	15,452	7,862	2,806	808
Observed number of SMN	92	64	34	11
SIR (95% CI)	10.2 (8.3–12.6)	5.7 (4.4–7.3)	3.5 (2.4–4.9)	2.4 (1.2–4.3)

SIR standardized incidence ratio, *95% CI* 95% confidence interval

The first is a cohort of 16,541 3-year survivors of childhood cancer treated in Britain between 1962 and 1987 (Jenkinson et al. 2004). Within this cohort of children diagnosed before the age of 15, 245 subsequent malignancies were identified, yielding an overall standardized incidence ratio (SIR) of 6.2 (95% confidence interval = 5.5–7.1). Of note, a statistically significant excess SIR was found within each decade of follow-up, with the overall SIR declining with successive decades from diagnosis (Table 46.2).

The second population-based study reported on a cohort of 47,697 children diagnosed before the age of 20 years, from the cancer registries of the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) during 1943–2005 (Olsen et al. 2009). Over this time period, 1,180 subsequent cancers were observed in 1,088 persons. The overall SIR was 3.3 (95% CI = 3.1–3.5). The relative risks were statistically significant at all ages, including cohort members up to the age of 70 years. Cohort members who were treated during the

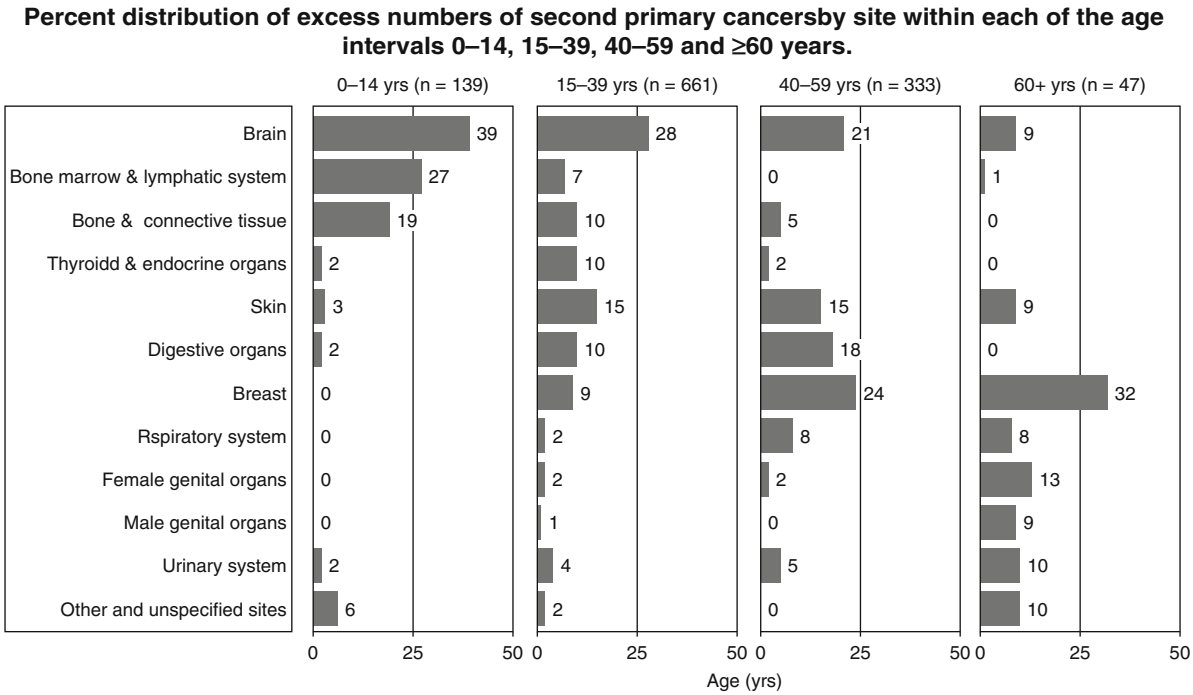

Fig. 46.1 Percent distribution of excess numbers of second primary cancers by site within each of the age intervals 0–14, 15–39, 40–59 and ≥60 years (Olsen et al. (2009))

multimodal treatment era (1975–2005) had the highest age-specific incidence rate of a subsequent cancer. Among survivors, the cumulative risks for second cancers before the age of 50 were 8.6% in the 1943–1959 subcohort (prechemotherapy era), 12.2% for the 1960–1974 subcohort (first-generation chemotherapy era), and 13.3% for the 1975–2005 subcohort (combination chemotherapy era). The number of excess second primary cancers observed by age is shown in Fig. 46.1, demonstrating continued increased risk decades of life after the original cancer diagnosis.

46.2.3 Childhood Cancer Survivor Study (CCSS)

The CCSS is a multi-institutional study of individuals who survived for 5 or more years after treatment for cancer diagnosed during childhood or adolescence. Eligibility criteria for CCSS are: diagnosis of leukemia, central nervous system (CNS) malignancies (all histologies), Hodgkin disease, non-Hodgkin lymphoma, malignant kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; diagnosis and initial treatment at one of the 26 collaborating CCSS institutions; and diagnosis between 1970 and 1986 (Robison et al. 2002).

The CCSS represents the largest cohort of relatively long-term survivors of childhood cancer and has contributed significantly because of the extensive medical record review of survivors and pathology validation of reported subsequent primary cancers. Because of the continued surveillance in this population, the 30-year cumulative incidence of the development of a subsequent primary cancer has been estimated to be 9.3% compared with the 20-year incidence in this cohort of 3.2% (Meadows et al. 2009). These data highlight the fact that the standardized incidence ratio continues to increase as this cohort ages.

A recent analysis within the CCSS cohort documented 802 subsequent malignant cancers among 732 survivors with a median time of follow-up since the primary cancer diagnosis of 22.9 years (range = 5.0–36.7 years) (Friedman et al. 2010). Associations between the primary cancer and subsequent cancers are shown in Table 46.3. The diagnosis of Hodgkin disease showed a disproportionate number of subsequent

Table 46.3 Original and subsequent malignant neoplasm diagnoses

Subsequent diagnosis		Leukemia			Lymphoma			CNS			Solid organ					Skin
		ALL	AML	Other	HL	NHL	Other	Glial	Medullo PNET	Other	Breast	Bone	STS	Thyroid	Other	Melanoma
Primary diagnosis	Number in cohort (%)															
Leukemia	4830 (33.6)	3	6		2	3	2	30	2	8	16	4	12	28	50	20
CNS tumors	1877 (13.1)		2	1	1		2	13	1	1	4	5	12	15	22	10
Hodgkin lymphoma	1927 (13.4)		8	6		10	6	4	1	3	161	6	26	42	69	13
Non-Hodgkin lymphoma	1080 (7.5)	2	2		3	1		2		5	6	2	4	10	16	2
Kidney	1256 (8.7)	2							1		7	4	8	3	12	3
Neuroblastoma	955 (6.7)	1	3		1			2			2		5	10	17	
Soft tissue sarcoma	2434 (17.0)		1	3	2			1		5	16	13	18	8	22	8
Bone tumors	1246 (8.7)	2	2	1				2		2	35	10	7	12	22	8
Total		10	24	11	9	14	10	54	5	24	247	44	92	128	230	64

Table 46.4 Observed and expected numbers of invasive second malignant neoplasms by second malignancy diagnosis

Second malignancy diagnosis	Cases observed	Cases expected	Standardized incidence ratio (95% C.I.)	Median time to SMN occurrence (years)
All invasive second malignancies	802	130	6.2 (5.7, 6.7)	17.8
Leukemia	41	130	6.2 (4.5, 8.4)	8.9
Acute lymphoblastic leukemia	10	7	3.7 (2.0, 6.8)	11.5
Acute myeloid leukemia	21	3	9.5 (6.2, 14.5)	7.4
Central nervous system	77	7	10.6 (8.5, 13.3)	13.2
Glial	52	6	9.0 (6.9, 11.9)	11.7
Medulloblastoma, PNET	6	0.6	7.6 (3.1, 18.3)	11.6
Meningioma (malignant)	11	0.04	91.3 (27.5, 302.8)	22.9
Breast cancer	188	17	10.7 (9.1, 12.6)	21.3
Melanoma	48	14	3.4 (2.5, 4.6)	18.9
Thyroid cancer	128	11	11.2 (9.4, 13.4)	18.6
Bone cancer	45	2	19.2 (14.4, 25.7)	9.8
Osteosarcoma	35	1	30.2 (21.4, 42.4)	9.3
Ewing sarcoma	4	0.6	6.7 (2.5, 17.9)	14.0
Lymphoma	33	18	1.8 (1.3, 2.6)	18.5
Hodgkin lymphoma	9	9	1.0 (0.5, 1.9)	18.5
Non-Hodgkin lymphoma	21	8	2.6 (1.6, 4.1)	21.6
Soft tissue sarcoma	73	9	8.2 (6.5, 10.4)	15.2
Kidney cancer	20	3	7.7 (4.8, 12.1)	19.6
Head and neck cancer	38	3	11.2 (8.1, 15.5)	15.6
Small intestine and colorectal cancer	27	6	4.9 (3.3, 7.1)	23.1
Lung and bronchus cancer	11	3	2.6 (2.0, 6.5)	20.3
Female genital cancer	23	10	2.2 (1.5, 3.3)	19.5
Other cancers	50	19	2.7 (2.0, 3.5)	21.0

cancers, with 35% of the reported subsequent malignant cancers in this group that only comprises 13% of the cohort. Standardized incidence ratios, using age-, sex-, and race-specific rates, found the highest risks were observed for subsequent bone cancer, thyroid cancer, head and neck cancer, CNS malignancies, and breast cancer (Table 46.4). Of particular interest is the increased risk of solid organ malignancies typically seen in older adults, such as head and neck tumors, small intestine and colorectal cancer, cancer of the lung and bronchus, and cancer of the female genital tract.

Earlier nested case-control studies of specific subsequent cancers have yielded important information regarding the influence of radiation dose on the occurrence of the more common subsequent cancers. In a study of 69 cases with confirmed thyroid cancer, a significant dose response of radiation to the risk of thyroid cancer increase up to 20–29 Gy of radiation (odds ratio (OR) = 9.8, 95% CI = 3.2–34.8), with a fall in the dose–response relationship at greater than 30 Gy, suggesting a cell-killing effect (Sigurdson et al. 2005). In a study of subsequent CNS tumors, the dose response for excess relative risk from radiation exposure for 40 subsequent gliomas was linear and peaked for doses of 30–44.9 Gy (OR = 21.0, 95% CI = 2.1–42.3) (Neglia et al. 2006). Similarly for a study of 120 subsequent breast cancer in female survivors, the odds ratio for breast cancer increased linearly with radiation dose, with the highest at doses 40 Gy (OR = 10.9, 95% CI = 3.8–31.0) (Inskip et al. 2006). For each of these subsequent cancers, chemotherapy for the first cancer diagnosis, exposure to chemotherapy, showed no association for the observed increase in risk.

46.3 Synopsis of Above Data

The development of subsequent primary cancers in pediatric cancer survivors is a rare occurrence but nonetheless of particular concern to survivors and their families.

The most common of these occurrences are subsequent cancers of the bone and soft tissue sarcomas, epithelial cancers (e.g., breast, head, and neck), thyroid, and melanoma. Each of the studies reported above show similar patterns, regardless of the makeup of the cohort being followed. First, exposure to radiotherapy increases the risk of certain cancers; however, chemotherapy also plays an important role. Second, the risk of the development of these subsequent cancers does not appear to diminish over the lifetime of the cancer survivor and is shown to stay increased through older adulthood. And, third, the type of subsequent cancer that develops appears to be determined by the therapeutic treatment of the original cancer and years since diagnosis.

These studies clearly indicate the need for careful surveillance and monitoring of subsequent cancers, from the time of completion of treatment through subsequent decades of life in pediatric cancer survivors. Recommendations for cancer surveillance have been outlined in the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, a collaborative effort within the Children's Oncology Group (COG Guidelines). These evidence-based guidelines are organized by therapeutic exposure and include a cancer screening section that lists elements of the history, physical exam, radiology, and other specialized tests that are recommended to aid in the detection of subsequent cancers in survivors. It is important to point out that many adult survivors do not realize the health risks that are related to their childhood cancer, and do not have regular medical follow-up or practiced recommended cancer screening (Kadan-Lottick et al. 2002). Continued education of cancer survivors and their health care providers is critical, to ensure this continued surveillance. Furthermore, continued follow-up of these described cohorts will continue to provide further insight into this increased risk decades after the original diagnosis.

46.4 Treatment of Rare Tumors as Secondary Tumors

Most secondary tumors in survivors of childhood cancer do not occur in childhood but rather in adulthood at an earlier age. However, a few specific secondary tumors are frequently encountered in childhood. Examples include sarcomas in patients with retinoblastoma and acute myelogenous leukemia in patients treated with etoposide. In both cases, standard treatment strategies must be directed against the secondary treatment. There are some limitations. Previous treatment may reduce the ability to deliver full doses of therapy such as radiation and anthracyclines. In the case of rare secondary tumors, pediatric oncologists, internal medicine oncologists, and primary physicians caring for patients who were childhood cancer survivors should be aware that tumors may occur at significant earlier ages. One goal of childhood cancer survivorship programs is education. Patients are informed of the need for close monitoring of their health. That is often not adequate as childhood cancer survivors often tend to avoid medical care. Ongoing education of the medical community is essential.

References

Curtis RE, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JF (eds) (2006) New malignancies among cancer survivors: SEER Cancer Registries, 1973–2000. National Cancer Institute, Bethesda

Friedman DL, Whitton J et al (2010) Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 102(14):1083–1095

Inskip PD, Ries LAD, Cohen RJ, Curtis RE (2006) New malignancies following childhood cancer, in. Curtis RE, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JF (eds). New malignancies among cancer survivors: SEER Cancer Registries, 1973–2000. National Cancer Institute, NIH Publ. No. 05-5302. Bethesda, MD, 2006, pp. 465-482

Jenkinson HC, Hawkins MM et al (2004) Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. Br J Cancer 91(11):1905–1910

Kadan-Lottick NS, Robison LL et al (2002) Childhood cancer survivors' knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study. JAMA 287(14):1832–1839

Kleinerman RA, Tucker MA et al (2005) Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol 23(10):2272–2279

Mariotto AB, Rowland JH et al (2009) Long-term survivors of childhood cancers in the United States. Cancer Epidemiol Biomarkers Prev 18(4):1033–1040

Meadows AT, Friedman DL et al (2009) Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 27(14): 2356–2362

Neglia JP, Robison LL et al (2006) New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 98(21):1528–1537

Ng AK, Kenney LB et al (2010) Secondary malignancies across the age spectrum. Semin Radiat Oncol 20(1):67–78

Oeffinger KC, Hudson MM (2004) Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin 54(4):208–236

Oeffinger KC, Mertens AC et al (2006) Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355(15):1572–1582

Olsen JH, Moller T et al (2009) Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 101(11):806–813

Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) (1999) Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program. NIH Publication No. 99–4649. National Cancer Institute, Bethesda

Robison LL, Mertens AC et al (2002) Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol 38(4):229–239

Sigurdson AJ, Ronckers CM et al (2005) Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet 365(9476):2014–2023

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