Pediatr Blood Cancer 2014;61:1202–1209

Rare Malignant Pediatric Tumors Registered in the German Childhood Cancer Registry 2001–2010

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Background. The German Childhood Cancer Registry (GCCR) annually registers approximately 2,000 children diagnosed with a malignant disease (completeness of registration >95%). While most pediatric cancer patients are diagnosed and treated according to standardized cooperative protocols of the German Society for Pediatric Oncology and Hematology (GPOH), patients with rare tumors are at risk of not being integrated in the network including trials and reference centers. ***Procedure.*** A retrospective analysis of all rare extracranial solid tumors reported to the GCCR 2001–2010 (age <18 years) was undertaken using a combination of the International Classification of Childhood Cancer (ICCC-3) and the International Classification of Diseases-Oncology (ICD-O-3). Tumors accounting for <0.3% of all malignancies were defined as rare (approx. 6 cases/year and registered malignancy). ***Results.*** According to this definition 1,189 rare extracranial solid tumors (18.2% of all malignant extracranial solid tumors) were registered, among these 232 patients (19.5% of rare tumor cases), were not included in preexisting GPOH studies/registries. Within 10 years, the number of registered non-GPOH-trial patients with a rare tumor increased. ***Conclusions.*** Though most of the GCCR-registered patients with rare malignant tumors are treated within GPOH trials, there is a considerable number of patients that have been diagnosed and treated outside the structures of the GPOH. These patients should be reported to the recently founded German Pediatric Rare Tumor Registry (STEP). Active data accrual and the development of appropriate structures will allow for better registration and improvement of medical care in these patients. Pediatr Blood Cancer 2014;61:1202–1209.

Key words: cancer registry; epidemiology; orphan disease; pediatric oncology; rare tumors; sarcomas

INTRODUCTION

Approximately 2,000 children and adolescents diagnosed with a malignant disease are registered within the German Childhood Cancer Registry (GCCR) annually [1]. During the last 40 years pediatric oncologists in Germany have managed to build a close network within the German Society for Pediatric Oncology and Hematology (GPOH). By promoting multicenter and interdisciplinary, national, and international cooperation risk-adapted treatment protocols have been developed, resulting in an impressive improvement in cure rates [2]. A close cooperation between clinical studies, reference centers, the GCCR, research groups and treating hospitals was established. Currently, more than 90% of all German children and adolescents under the age of 15 years with malignant diseases are enrolled into therapeutic trials and clinical registries and reported to the GCCR [3,4]. This clinical and translational work led to an increasing understanding of pediatric tumors.

In contrast, it is assumed that a substantial proportion of patients with rare pediatric tumors are insufficiently captured by the presently available structures so far. Even though many German patients affected by rare pediatric tumors have already been registered with and treated according to guidelines of therapy optimization trials (Table I), it is estimated that still about 8–15% of patients with rare tumors are not treated according to standardized cooperative treatment protocols and may not even be consulted by a pediatric oncologist [5–8]. Therefore, these patients are excluded from the well-developed network of the GPOH. As a result, no clinical or scientific structures have been developed to ensure accurate diagnosis and evidence based treatment, research projects appear to be impossible due to the rarity of these entities, and the interest of the pharmaceutical industry to develop and evaluate new drugs for these entities is rather limited [9,10].

Thus several European pediatric oncology groups have founded registries and study groups focusing on previously unregistered rare pediatric tumors [9,11,12]. The German Pediatric Rare Tumor Group (STEP) was founded in 2006, and registration for the entities not considered in the existing GPOH-trials within a consultation network was started in 2008 [13]. In the same year the existing national groups within Europe formed a new cooperative group (EXPeRT—European Cooperative Study Group for Pediatric Rare Tumors) [12]. These initiatives led to increased awareness of

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Grant sponsor: German Childhood Cancer Foundation ("Deutsche Kinderkrebsstiftung"), Bonn, Germany; Grant sponsor: "Verein zur Förderung des Tumorzentrums Erlangen", Erlangen, Germany

Conflict of interest: Nothing to report.

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Received 24 June 2013; Accepted 28 January 2014

DOI 10.1002/pbc.24997
Published online 28 February 2014 in Wiley Online Library (wileyonlinelibrary.com).

TABLE I. Overview of Study Groups Prospectively Registering Rare Pediatric Extracranial Tumors within the Society of Pediatric Oncology and Hematology

Rare tumor entities	Clinical trial center/Registry
Rare soft tissue sarcomas and bone tumors	SoTiSar Registry of the German CWS, COSS, and EICESS study groups (Prof. Dr. E. Koscielniak, Prof. Dr. T. Klingebiel, Prof. Dr. S. Bielack, Prof. Dr. H. Jürgens)
Rare gonadal tumors	German MAKEI study group (Dr. G. Calaminus, Prof. Dr. D. Schneider)
Endocrine tumors	MET Registry (Prof. Dr. P. Vorwerk)
Rare liver tumors	German Cooperative Pediatric Liver Tumor Study Group (Prof. Dr. D. v. Schweinitz)
Esthesioneuroblastoma	German Neuroblastoma Study Group (Prof. Dr. med. F. Berthold)
Gastrointestinal stromal tumors	SoTiSar Registry (PD Dr. M. Benesch)
Nasopharyngeal carcinoma	German NPC study group (Prof. Dr. R. Mertens)
Rare renal tumors	SIOP/GPOH Nephroblastoma Study Group (Prof. Dr. N. Graf)
Rhabdoid tumors	EU-RHAB Registry (Prof. Dr. M. Frühwald)
Pleuropulmonary blastoma	SoTiSar Registry (Dr. S. Kirsch)

SoTiSar, registry for soft tissue sarcoma and other soft tissue tumors in children, adolescents, and young adults; CWS, Cooperative Weichteilsarkom Studiengruppe; COSS, Cooperative Osteosarcoma Study Group; EICESS, European Intergroup Cooperative Ewing Sarcoma Studies; MAKEI, German Pediatric Germ Cell Tumor Study Group; MET, Registry for Malignant Endocrine Tumors in Children and Adolescents; NPC, German Nasopharyngeal Carcinoma Study Group; SIOP, International Society of Pediatric Oncology; GPOH, German Society of Pediatric Oncology and Hematology; EU-RHAB, European Registry for Rhabdoid Tumors.

pediatric rare tumors, and a competence network could be built in a short time providing support for clinical management of patients with rare tumors and fostering research in the field.

This manuscript describes the specific structures for rare pediatric tumors within Germany, and gives a broad overview of all rare solid pediatric tumors outside the CNS differentiating between entities enrolled in the existing clinical trials or registries and those which lie in the focus of the recently founded rare pediatric study groups.

METHODS

The German Childhood Cancer Registry (GCCR) is a population based registry. Since its initiation in 1980, all children <15 years with malignant diseases and residency in the Federal Republic of Germany at the time of diagnosis have been included. Patients ≥ 15 and <18 years were sporadically reported before 2009 and systematically since then. In 1991 the registry was extended to the area of the former German Democratic Republic (GDR). The completeness of registration is estimated to be 95% for patients until the age of 15 years [14]. Patients and/or their guardians have given their consent to registration. The families are committed to the goals of the registry and therefore only about 1% do not give their consent, another about 1% are missing for other reasons [14]. In case of missing permission, cases are registered anonymously with some minimum information in order to be able to calculate incidence rates. Close cooperation with GPOH, its clinical trials and the treating hospitals allows for high data quality, exact diagnosis confirmed by reference pathology and additional registration of clinical data such as grading and immunological subtypes. Over 90% of the patients registered are included in clinical trials of the GPOH [1,14]. Classification of the pediatric malignancies registered with the GCCR is based on the International Classification of Childhood Cancer 3rd edition (ICCC-3) [15].

We present an overview of all rare extracranial solid tumors reported to the GCCR between 2001 and 2010 (age <18 years). All extracranial solid tumors accounting for less than 0.3% of all malignant diseases were defined as rare (not more than six cases per year and registered malignancy on average). We chose this cut-off point for the purpose of the article as we found this to be the threshold just including all entities generally considered as rare pediatric tumors. We were especially interested to understand, which other entities (not included in the group of rare pediatric tumors in the closer sense so far) appear to have the same incidence by drawing this line. These tumors have been registered in pediatric clinical trials in Germany for years and therefore do not fall into the definition of rare pediatric tumors mentioned above. As the specific spectrum of rare cancers in children is not well described through one of the existing classification systems, a combination of the third version of the ICCC-3 [15] and the International Classification of Diseases-Oncology (ICD-O) [16] was used to identify cases. Total and relative numbers, age distribution, two time periods of registration (2001–2005, 2006–2010) and registration into a GPOH trial or registry are reported. In addition, total numbers and age distribution of entities, which are typically not registered within a GPOH study or registry, but should consequently be registered with the recently founded German Pediatric Rare Tumor Registry (STEP), are shown. These cases are termed non-GPOH-trial patients.

RESULTS

Between 2001 and 2010, the GCCR registered 20,974 malignancies in children <18 years. Among these, 6,532 patients (31.1% of all malignancies) were diagnosed with solid tumors outside the central nervous system. According to the above mentioned definition of rarity ($<0.3\%$ of all malignancies), 1,189 rare tumors were identified (5.7% of all malignancies; 18.2% of all malignant extracranial solid tumors). The distribution within the ICCC-3-groups was as follows: 69 rare extracranial solid tumors were identified within the ICCC-3-group IV Neuroblastoma and other peripheral and intraspinal neoplasms, 53 within ICCC-3-group VI Renal tumors, 48 within ICCC-3-group VII Hepatic tumors, 101 within ICCC-3-group VIII Malignant bone tumors, 359

within ICCC-3-group IX Soft tissue and other extraosseous sarcomas, 276 within ICCC-3-group X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads, 262 within ICCC-3-group XI Other malignant epithelial neoplasms and malignant melanomas, and 21 within ICCC-3-group XII Other and unspecified malignant neoplasms (Fig. 1).

Not registered within a trial or registry of the GPOH were 249 (20.9%) out of these 1,189 rare tumors. These tumors would now qualify for registration in the recently founded STEP Registry (so called non-GPOH-trial patients). This accounts for 1.2% of all malignancies or 3.8% of all malignant extracranial tumors registered within the GCCR. Figure 2 gives an overview of these entities. Following the ICCC-3, most non-GPOH-trial patients can be classified as XI(d) Malignant Melanomas (n = 55) and XI(f) Other and Unspecified Carcinomas (n = 120). The age distribution of non-GPOH-trial patients demonstrated a predominance of adolescents older than 9 years (see Table II and Fig. 3). Over a period of 10 years, no incidence trend is seen. Within the time periods 2001–2005 and 2006–2010 a total of 10,549 and 10,425 patients with malignant diseases were registered, respectively. The number of registered patients with extracranial solid tumors remained also unchanged (2001–2005: 3,322 cases; 2006–2010: 3,210 cases). At the same time the number of registered non-GPOH-trial patients with a rare tumor increased. Between years 2001 and 2005 106 non-GPOH trial patients were reported to the GCCR, while for the time period between 2006 and 2010 143 were identified. This increase of registrations within the last 5 years can be explained by a higher number of reported melanomas (2001–2005: n = 13; 2006–2010: n = 42) and salivary gland tumors (2001–2005: n = 4; 2006–2010: n = 19). Out of the latter 31 cases (26%) were indicated to be reported to the STEP Registry.

DISCUSSION

Pediatric oncologists have increasingly realized that there are several tumor entities, which they might see once only in their lifetime practice. Optimal care for these patients poses a great challenge as no guidelines for diagnosis and treatment exist for the pediatric age group. There have been efforts to define this very heterogeneous group of rare pediatric tumors. Though many of these entities are classified as other malignant epithelial neoplasms and melanomas according to the ICCC-3 subgroup XI, rare pediatric tumors cannot be reduced to this category [17]. By doing so, many pediatric rare tumors as pleuropulmonary blastoma, pancreatoblastoma, or sex cord stromal tumors are excluded. On the other hand, there are several entities occurring in children such as many soft tissue sarcomas and germ cell tumors, which show a very low incidence, but have been registered in pediatric clinical trials in most developed countries for years and therefore are not in the focus of the pediatric rare tumor groups. Considering that the pediatric rare tumors we are focusing on are not only very rare but also orphan entities, the Italian TREP project (Italian Study on Rare Tumors in Pediatric Age) pragmatically defined pediatric rare tumors as "any malignancy characterized by an annual incidence <2/million and not considered in other trials" [6]. The STEP working group adopted this definition, when the project was launched in 2006 aiming at an infrastructure for children and adolescents with rare tumors [13]. Since then, this arbitrary definition has been cited

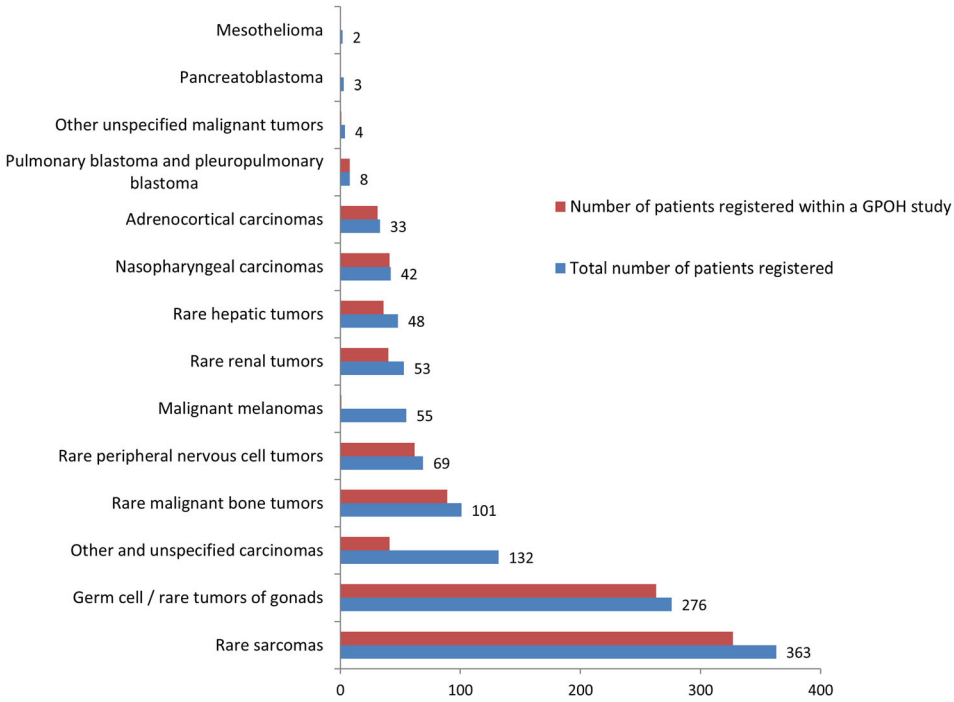

Fig. 1. Overview of 1,189 rare extracranial solid tumors defined as <0.3% of all malignancies registered within the German Childhood Cancer Registry (GCCR) 2001–2010. Total numbers under the age of 18 and numbers of patients registered within a study of the German Society of Pediatric Oncology and Hematology (GPOH) are indicated. Leukemias, lymphomas, and CNS tumors are excluded.

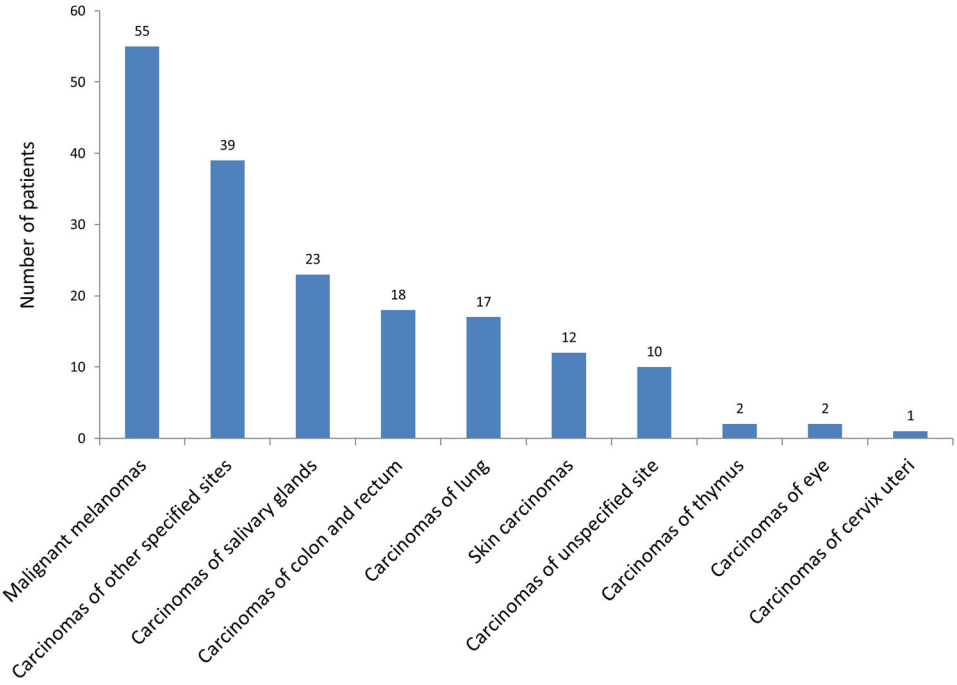

Fig. 2. Overview of 179 cases of malignant epithelial neoplasms and malignant melanomas typically not registered within studies of the German Society of Pediatric Oncology and Hematology (GPOH) and registered within the German Childhood Cancer Registry (GCCR) 2001–2010. Total numbers under the age of 18 are indicated. Note: Adrenocortical carcinomas and carcinomas of the appendix were excluded as they are registered within the Study Registry for Malignant Endocrine Tumors in Children and Adolescents (MET) and nasopharyngeal carcinomas were excluded as they are registered within the German Nasopharyngeal Carcinoma Study Group (NPC).

repeatedly and some characteristics of rare pediatric tumors have been added: "Rare pediatric malignancies are characterized by an annual incidence <2/1,000,000 and/or are considered as orphan due to a lack of pediatric trials and/or underestimation of incidence. Rare pediatric malignancies might be common in the adult age, often an underlying genetic predisposition can be suspected, and they might be inadequately diagnosed and treated" [5]. According to this definition it is estimated that, depending on national structures within European countries, about 8–15% of all pediatric patients with a malignancy fall into this category [5–7].

Given that rare pediatric tumors have to be considered as orphan disease and are not defined by a numerical cut-off point or specific pathology only [12], we used this analysis to understand the spectrum of entities upon which the STEP registry should concentrate. While we arbitrarily considered all malignancies accounting for less than 0.3% of all malignant diseases to be rare, before choosing this cut-off point, we made sure that all entities generally considered as rare pediatric tumors according to the above mentioned definition were included. Of the 1,189 identified cases, 79.1% were registered within GPOH trials or registries (Table I). Because most of these rare tumors are soft tissue tumors/sarcoma and germ cell tumors, these patients have typically been diagnosed and treated within the German Cooperative Soft Tissue Sarcoma Group (CWS) [18] and German Pediatric Germ Cell Tumor Study Group (MAKEI) trials [19], and specific treatment protocols have been available for decades. However, these tumors have been identified as rare tumors only as a result of our algorithm. Their identification as rare tumors is only explained by the extreme heterogeneity of the clinical and histopathological classification. Thus, both soft tissue sarcomas and germ cell tumors may present at many anatomical sites and with highly variable histology. Unfortunately, different site-specific classification systems further complicate categorization. For instance, germinomatous tumors, including seminoma of the testis, dysgerminoma of the ovary, and germinoma of the CNS, have been divided into six subgroups, each including 1–51 tumors. However, they are histologically and genetically undistinguishable [20]. Their total number is 112 (0.5%), which would not qualify them as rare according to our algorithm. In almost the same manner the large Ewing family of tumors includes Ewing tumors of bone, extraosseous Ewing tumors, and primitive neuroectodermal tumors of bone and soft tissue (PNET). These tumors all come from the same type of stem cell. The ICCC-3 [15] is not accurate for rare pediatric tumors and may possibly have to be revised with regard to this specific aspect. There have been efforts to develop a separate nosologic system for malignant entities occurring in adolescents and young adults [21]. This system might be used as a basis for the development of a new classification system for pediatric rare tumors, which mainly occur in adolescents and therefore show a similar spectrum.

In accordance with this consideration, most of the rare bone tumors, rare peripheral nervous cell tumors, rare hepatic tumors, and rare renal tumors have been registered within GPOH trials. Though specific therapy protocols were not always available, patients may profit from the competence structures of these studies. In contrast to many other European countries, we can additionally benefit from years of experiences of two rare pediatric tumor study groups: the Malignant Endocrine Tumors in Children and Adolescents Study (MET) and the German Nasopharyngeal

TABLE II. Rare Extracranial Solid Tumors Registered Within the German Childhood Cancer Registry 2001–2010

	<18		0–4	5–9	10–14	15–17	GPOH study	
Age	No[a]	%	No[a]	No[a]	No[a]	No[a]	No[b]	%
All malignancies	20,974	100	7,951	4,823	5,179	3,021	19,523	
IV. Neuroblastoma and other peripheral and intraspinal neoplasms								
Ganglioneuroblastoma	54	0.26	29	23	2	0	54	100
Paraganglioma, malignant	1	0.01	0	0	0	1	0	0
Pheochromocytoma	1	0.01	0	0	0	1	1	100
Medulloepithelioma	4	0.02	2	0	2	0	2	50
Olfactory neuroblastoma	9	0.04	3	1	2	3	5	56
VI. Renal tumors								
Malignant rhabdoid tumor	13	0.26	12	1	0	0	10	77
Clear cell sarcoma of kidney	9	0.04	3	3	1	2	9	100
Peripheral neuroectodermal tumor	1	0.01	0	0	1	0	1	100
Papillary adenocarcinoma, NOS	10	0.05	0	1	9	0	8	80
Renal cell carcinoma	20	0.10	1	5	8	6	12	60
VII. Hepatic tumors								
Carcinoma, NOS	1	0.01	0	0	0	1	0	0
Cholangiocarcinoma	1	0.01	0	0	1	0	0	0
Hepatocellular carcinoma	42	0.20	3	11	19	9	32	76
Neuroendocrine carcinoma	2	0.01	0	0	2	0	2	100
Unspecified malignant hepatic tumors	2	0.01	1	0	1	0	2	100
VIII. Malignant bone tumors								
Chondrosarcomas	14	0.07	0	2	11	1	9	64
Peripheral neuroectodermal tumor of bone	62	0.30	9	16	18	19	62	100
Malignant fibrous neoplasms of bone	4	0.02	0	0	2	2	4	100
Malignant chordomas	9	0.04	2	5	2	0	8	89
Odontogenic malignant tumors	1	0.01	1	0	0	0	1	100
Miscellaneous malignant bone tumors	4	0.02	0	0	1	3	1	25
Unspecified malignant bone tumors	7	0.03	0	1	4	2	4	57
IX. Soft tissue and other extraosseous sarcomas								
Fibrosarcoma	19	0.09	4	5	6	4	18	95
Fibromyxosarcoma	14	0.07	2	1	6	5	14	100
Infantile fibrosarcoma	24	0.11	23	0	1	0	24	100
Myofibroblastic sarcoma	10	0.05	4	1	5	0	6	60
Hemangiopericytoma, malignant	2	0.01	1	0	1	0	2	100
Malignant peripheral nerve sheath tumor	59	0.28	7	10	25	17	50	85
Neurilemmoma, malignant	3	0.01	0	1	2	0	3	100
MPNST with rhabdomyoblastic differentiation	2	0.01	0	0	2	0	1	50
Kaposi sarcoma	2	0.01	0	0	1	1	0	0
Askin tumor	7	0.03	1	2	2	2	7	100
Peripheral neuroectodermal tumor	60	0.27	15	15	19	11	58	97
Extrarenal rhabdoid tumor	29	0.14	20	2	4	3	22	76
Liposarcomas	7	0.03	0	0	2	5	7	100
Fibrous histiocytoma, malignant	6	0.03	0	3	2	1	5	83
Dermatofibrosarcoma, NOS	21	0.10	9	4	5	3	20	95
Leiomyosarcomas	9	0.04	1	1	5	2	9	100
Clear cell sarcoma	16	0.08	3	3	8	2	14	88
Hemangiosarcoma	5	0.02	0	1	3	1	5	100
Hemangioendothelioma, malignant	2	0.01	1	0	1	0	2	100
Lymphangiosarcoma	1	0.01	0	0	0	1	1	100
Chondrosarcoma	13	0.06	3	4	3	3	12	92
Alveolar soft part sarcoma	17	0.08	1	2	7	7	16	94
Desmoplastic small round cell tumor	22	0.11	0	5	14	3	19	86
Myxosarcoma	4	0.02	2	0	2	0	3	75
Rhabdomyosarcoma with ganglionic differentiation	4	0.02	3	0	0	1	4	100
Mesenchymoma, malignant	1	0.01	1	0	0	0	1	100
X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads								
Dysgerminoma, extragonadal sites	4	0.02	0	2	0	2	4	100
Seminoma, extragonadal sites	1	0.01	0	0	0	1	1	100
Germinoma, extragonadal sites	23	0.11	10	1	6	6	21	91
Yolk sac tumor, extragonadal sites	47	0.22	46	0	1	0	46	98

TABLE II. (*Continued*)

	<18		0–4	5–9	10–14	15–17	GPOH study	
Age	No[a]	%	No[a]	No[a]	No[a]	No[a]	No[b]	%
Choriocarcinoma, extragonadal sites	5	0.02	1	0	4	0	4	80
Mixed germ cell tumor, extragonadal sites	6	0.03	4	1	0	1	6	100
Dysgerminoma	51	0.24	0	10	21	20	51	100
Seminoma	5	0.02	0	0	0	5	3	60
Germinoma	28	0.13	2	2	8	16	27	96
Malignant gonadal embryonal carcinoma	16	0.08	0	1	5	10	16	100
Malignant gonadal choriocarcinoma	14	0.08	0	1	12	1	14	100
Malignant gonadal tumors of mixed forms	60	0.29	4	6	25	25	60	100
Gonadal carcinomas	11	0.05	0	1	4	6	6	55
Other and unspecified malignant gonadal tumors	5	0.02	0	0	0	5	4	80
XI. Other malignant epithelial neoplasms and malignant melanomas								
Adrenocortical carcinomas	33	0.16	15	8	6	4	31	94
Nasopharyngeal carcinomas	42	0.20	0	1	23	18	41	98
Malignant melanomas	55	0.26	13	12	23	7	1	2
Skin carcinomas	12	0.06	0	3	4	5	0	0
XI (f) Other and unspecified carcinomas								
Carcinomas of salivary glands	23	0.11	0	4	14	5	1	4
Carcinomas of colon and rectum	18	0.09	0	1	9	8	0	0
Carcinomas of appendix	8	0.04	0	1	3	4	8	100
Carcinomas of lung	17	0.08	0	2	6	9	10	59
Carcinomas of thymus	2	0.01	0	0	2	0	0	0
Carcinomas of cervix uteri	1	0.01	0	0	1	0	0	0
Carcinomas of eye	2	0.01	0	0	2	0	0	0
Carcinomas of other specified sites	39	0.19	1	3	20	15	16	41
Carcinomas of unspecified site	10	0.05	2	0	3	5	6	60
XII. Other and unspecified malignant neoplasms								
Gastrointestinal stromal tumor	2	0.01	0	0	2	0	2	100
Pancreatoblastoma	3	0.01	0	2	0	1	0	0
Pulmonary blastoma/pleuropulmonary blastoma	8	0.04	8	0	0	0	8	100
Endometrial stromal sarcoma	1	0.01	0	0	1	0	1	100
Stromal sarcoma, NOS	1	0.01	1	0	0	0	1	100
Mesothelioma	2	0.01	0	0	1	1	0	0
Other unspecified malignant tumors	4	0.02	0	0	4	0	1	25
Total	1,189	5.67	274	191	422	302	940	97

Rare extracranial solid tumors were defined as <0.3% of all malignancies. [a]Total and relative numbers under the age of 18 and within age groups 0–4, 5–9, 10–14, and 15–17 are shown. [b]Registration within a study of the German Society of Pediatric Oncology and Hematology (GPOH) is indicated. Leukemias, lymphomas, and CNS tumors are excluded. Cases were grouped according to the International Classification of Diseases-Oncology (ICD-O) and the third version of the International Classification of Childhood Cancer (ICCC-3).

Carcinoma Study Group (NPC), both were founded in the Nineties [22–25]. Therefore, compared to other national pediatric oncology groups, the infrastructure for rare tumors in children and adolescents is very well developed in Germany. For many entities, the integration into the network of the GPOH has already been achieved, and reporting of these patients to the GCCR proved to be beneficial [1,3].

Nevertheless, a group of patients with rare tumors remains excluded from the diagnostic, therapeutic, and scientific network of the GPOH so far and the STEP Registry focuses in particular on these non-GPOH trial patients. The epidemiology of these rare pediatric tumors is widely unknown. In our analysis, we identified 232 patients (19.5% of rare tumor cases), who were not registered within another study or registry of the GPOH. This accounts for 1.2% of all malignancies registered or 3.8% of all malignant extracranial tumors. The numbers are, therefore, lower than estimated [5–8]. Based on an analysis rom the Surveillance, Epidemiology and End Result (SEER) data base of the U.S. National Cancer Institute, the Infrequent Tumor Initiative of the U.S. Children's Oncology Group reports a higher incidence of rare tumors. In this analysis rare tumors account for approximately 15% of all cancers in the age group <15 years and 30% <20 years [8,17].

The reasons for these differences in reporting numbers of rare tumors in children and adolescents arise from the rarity of the entities. Some patients with rare tumors might not be reported to registries for reasons lying in the organizational structures within different countries. Following the ICCC-3 [15], most cases of rare tumors identified through our analysis can be classified as XI(d) Malignant Melanomas (n = 55) and XI(f) Other and Unspecified Carcinomas (n = 120), predominantly adult cancer subtypes. It can be assumed that these patients are therefore mainly treated outside of pediatric oncologic structures, for example, in other disciplines like surgery, ear-nose-throat (ENT), and dermatology. While the compliance to report patients treated within pediatric oncology departments to the GCCR is generally good, this might not be the

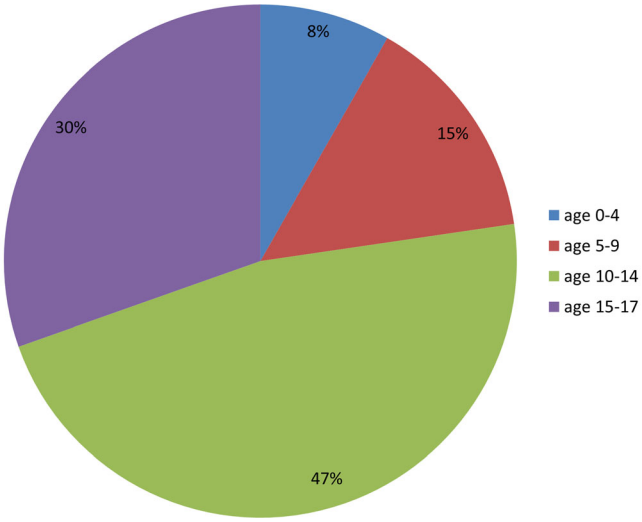

Fig. 3. Age distribution of patients with rare extracranial solid tumors not registered within studies of the German Society of Pediatric Oncology and Hematology (GPOH) and registered within the German Childhood Cancer Registry (GCCR) 2001–2010. Relative numbers within age groups 0–4, 5–9, 10–14, and 15–17 are shown. Note: Patients within age group 15–17 were only systematically registered since 2009.

case for patients treated outside the close network of the pediatric societies [13]. In this context, it is also remarkable, that since the MAKEI group published several reports on sex cord stromal tumors, an annual reporting of 10–15 patients with such rare gonadal tumors to the MAKEI study has been achieved (personal communication co-author D. Schneider). However, only a few of these tumors are reported in this analysis, which means they were incompletely reported to the GCCR. This might be related to the fact that some of these patients have been exclusively been treated in gynecology departments, with lower adherence to GCCR registration. Moreover, this illustrates that rarity of tumors in a clinical sense is not only defined by their small numbers within epidemiological and pathological categories but also by their clinical status as orphan disease.

Because of the limited experience with rare tumor types and the lack of central pathologic review diagnostic and coding inconsistencies may exist [26]. Thus the classification of entities into benign, borderline, and malignant neoplasms might not be uniform [27].

The incidence of rare pediatric tumors dramatically rises in the second decade of life, while pediatric cancer registries have a tradition to register only children under the age of 15 years. Realizing this gap the GCCR extended their age of registration to $<$18 years in 2009. Anyway, before 2009 children aged 15 and were only sporadically registered. Therefore the presented numbers for patients $\geq$15 years do not reflect true incidence of these entities. This is especially evident for histotypes typically occurring in young adults as hepatocellular carcinoma (9/42 cases are aged 15 or older) or malignant melanoma (7/55 aged 15 or older). Despite this obvious registration gap, the age distribution of patients with rare tumors typically not registered within studies of the GPOH showed a clear predominance of cases over the age of 9 years (see Table II and Fig. 3). Thus, after extension of the registration for patients until the age of 18 years, we can expect to register a significant higher number of rare tumors the following years.

A near to complete reporting of childhood cancer patients treated within pediatric oncology departments to the GCCR for years has already been achieved long ago. Nevertheless, registration of non-GPOH-trial patients with tumors typically treated outside the structures of the GPOH (e.g., melanomas and salivary gland tumors) could be increased after the launch of STEP in 2006. Despite this first success we have to assume that we still do not register most of the pediatric patients treated in other disciplines than pediatric oncology, let alone in outpatient departments [5,17]. While in our analysis 31 cases (25%) were indicated to be registered within the STEP between 2006 and 2010, the STEP Registry itself reports 120 patients registered between October 2008 and March 2011 [11]. These gaps have to be closed in order to get a complete picture of rare tumors in children and adolescents. Furthermore, health care structures for patients with these orphan diseases have to be improved and interdisciplinary and international networks have to be expanded. Additionally, the attention for rare entities within the pediatric oncology has to be further raised and structures have to be adapted. The aim is a step-by-step registration of detailed clinical data for every single patient in order to obtain valid data through clinical research projects. Active prospective registration to the STEP Registry, which was formally launched by the GPOH in 2012 will allow for a better registration in the future.

ACKNOWLEDGMENT

The STEP Registry is supported by the German Childhood Cancer Foundation (“Deutsche Kinderkrebsstiftung”), Bonn, Germany and the “Verein zur Förderung des Tumorzentrums Erlangen”, Erlangen, Germany. We also wish to thank all patients for participating in the studies and registries of the GPOH and our colleagues performing documentations for our patients. We thank the members of the STEP Registry for their continued work for patients with rare tumors in childhood and adolescents.

REFERENCES

1. Kaatsch P, Spix C. German Childhood Cancer Registry—Annual Report 2011 (1980–2010). Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz wwwkinderkrebsregisterde 2012.
2. Creutzig U, Henze G, Bielack S, et al. Krebserkrankungen bei Kindern: Erfolg durch einheitliche Therapiekonzepte seit 25 Jahren. Dtsch Arztebl 2003;100:A842–A852.
3. Creutzig U, Zimmermann M, Hannemann J, et al. Quality management within the competence network of paediatric oncology and haematology. Klin Padiatr 2003;215:338–340.
4. Rossig C, Juergens H, Schrappe M, et al. Effective childhood cancer treatment: The impact of large scale clinical trials in Germany and Austria. Pediatr Blood Cancer 2013;60:1574–1581.
5. Brecht IB, Kaatsch P. Epidemiology. In: Schneider DT, Brecht IB, Olson TA, Ferrari A, Rare tumors in children and adolescents. Berlin Heidelberg: Springer; 2012.
6. Ferrari A, Bisogno G, De Salvo GL, et al. The challenge of very rare tumours in childhood: The Italian TREP project. Eur J Cancer 2007;43:654–659.
7. Brennan B, Stiller C. Rare tumors. In: Estlin EJ, Gilbertson RJ, Wynn RF, editor. Pediatric hematology and oncology. Chichester, West Sussex, UK: Blackwell Publishing Ltd; 2010.
8. Ries LA, Smith MA, Gurney JG. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. Bethesda: National Cancer Institute; 1999.
9. Bisogno G, Ferrari A, Bien E, et al. Rare cancers in children—The EXPeRT initiative: A report from the European Cooperative Study Group on pediatric rare tumors. Klin Padiatr 2012;224:416–420.
10. Schneider DT, Brecht IB. Care for rare cancers: Improved care requires improved communication. Klin Padiatr 2010;222:124–126.
11. Brecht IB, Schneider DT. National and International Study Groups. In: Schneider DT, Brecht IB, Olson TA, Ferrari A, editors. Rare tumors in children and adolescents. Heidelberg Berlin: Springer; 2012. 95–118.
12. Ferrari A, Schneider DT, Bisogno G. The founding of the European Cooperative Study Group on Pediatric Rare Tumors—EXPeRT Expert Rev Anticancer Ther 2013;13:1–3.
13. Brecht IB, Graf N, Schweinitz D, et al. Networking for children and adolescents with very rare tumors: Foundation of the GPOH Pediatric Rare Tumor Group. Klin Padiatr 2009;221:181–185.
14. Kaatsch P, Spix C. German Childhood Cancer Registry—Annual Report 2011 (1980–2010). In.: Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University Mainz 2012.
15. Steliarova-Foucher E, Stiller C, Lacour B, et al. International classification of childhood cancer, third edition. Cancer 2005;103:1457–1467.

16. Fritz AG, Percy C, Jack A, et al. International classification of diseases for oncology (ICD-O), 3rd edition. Geneva: World Health Organization; 2000.
17. Pappo AS, Krailo M, Chen Z, et al. Infrequent tumor initiative of the Children's Oncology Group: Initial lessons learned and their impact on future plans. J Clin Oncol 2010;28:5011–5016.
18. Weihkopf T, Blettner M, Dantonello T, et al. Incidence and time trends of soft tissue sarcomas in German children 1985–2004—A report from the population-based German Childhood Cancer Registry. Eur J Cancer 2008;44:432–440.
19. Hofmann M, Schlegel PG, Hippert F, et al. Testicular sex cord stromal tumors: Analysis of patients from the MAKEI study. Pediatr Blood Cancer 2013;60:1651–1655.
20. Oosterhuis JW, Looijenga LH. Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer 2005;5:210–222.
21. Birch JM, Alston RD, Kelsey AM, et al. Classification and incidence of cancers in adolescents and young adults in England 1979–1997. Br J Cancer 2002;87:1267–1274.
22. Mertens R, Granzen B, Lassay L, et al. Treatment of nasopharyngeal carcinoma in children and adolescents: Definitive results of a multicenter study (NPC-91-GPOH). Cancer 2005;104:1083–1089.
23. Redlich A, Boxberger N, Strugala D, et al. Systemic treatment of adrenocortical carcinoma in children: Data from the German GPOH-MET 97 trial. Klin Padiatr 2012;224:366–371.
24. Boxberger N, Redlich A, Boger C, et al. Neuroendocrine tumors of the appendix in children and adolescents. Pediatr Blood Cancer 2013;60:65–70.
25. Redlich A, Wechsung K, Boxberger N, et al. Extra-appendiceal neuroendocrine neoplasms in children—Data from the GPOH-MET 97 Study. Klin Padiatr 2013;225:315–319.
26. Pastore G, De Salvo GL, Bisogno G, et al. Evaluating access to pediatric cancer care centers of children and adolescents with rare tumors in Italy: The TREP project. Pediatr Blood Cancer 2009;53:152–155.
27. Stiller CA. International patterns of cancer incidence in adolescents. Cancer Treat Rev 2007;33:631–645.