Rare Cancers in Children – The EXPeRT Initiative: A Report from the European Cooperative Study Group on Pediatric Rare Tumors

Seltene Tumoren bei Kindern – die EXPeRT Initiative: Ein Bericht der European Cooperative Study Group on Pediatric Rare Tumors

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Abstract

The low incidence and the heterogeneity of very rare tumors (VRTs) demand for international cooperation. In 2008, EXPeRT (European Cooperative Study Group for Pediatric Rare Tumors) was founded by national groups from Italy, France, United Kingdom, Poland and Germany. The first aims of EXPeRT were to agree on a uniform definition of VRTs and to develop the currently most relevant scientific questions. Current initiatives include international data exchange, retrospective and prospective studies of specific entities, and the development of harmonized and internationally recognized guidelines. Moreover, EXPeRT established a network for expert consultation to assist in clinical decision in VRTs.

Zusammenfassung

Seltene Tumoren zeichnen sich nicht nur durch eine niedrige Inzidenz sondern auch durch ihre ausgeprägte eine klinische und histologische Heterogenität aus. Um die Forschungsaktivitäten auf diesem Gebiet zu unterstützen, wurde 2008 eine internationale Arbeitsgruppe, die European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT), gegründet. In ihr kooperieren die Arbeitsgruppen aus Italien, Frankreich, Großbritannien, Polen und Deutschland. Als erstes Ziel wurden eine einheitliche Definition der Seltenen Tumoren entwickelt und wissenschaftliche Fragestellungen formuliert. Aktuelle Initiativen beinhalten den Datenaustausch und gemeinsame retro- und prospektive Analysen für bestimmte Entitäten. Darüber hinaus wird eine Vereinheitlichung der Behandlungsempfehlungen für Seltene Tumoren angestrebt. Auf dieser Grundlage baut EXPeRT ein klinisches und wissenschaftliches Konsiliarnetz auf, das anfragende Kliniken bei anstehenden klinischen Entscheidungen bei Kindern und Jugendlichen mit seltenen Tumoren unterstützt.

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Introduction: very rare tumors as orphan disease

Cancer in children is rare, and hence pediatric oncologists have expertise in rare cancers. Over the years, they have been able to continuously improve treatment, perform research, raise interest and find support. The impossibility to perform meaningful studies on the few patients treated in each pediatric oncology center has fostered the foundation of national and international networks and the initiation of international cooperative studies. The results of this increasing collaboration are evident in the continuous improvement in outcome for almost all pediatric tumors. Nevertheless, there remains a small but significant group of children, which unfortunately, did not benefit to the same extent from this enormous achievement. This group primarily includes those children who suffer from very rare tumors (VRT). These might be classified as orphan diseases, which by definition indicates that neither clinical nor scientific structures have been developed to aid in their diagnosis and treatment [7, 15].

The group of pediatric VRTs is extremely heterogeneous involving different organ sites and many histological tumor types. Some are characteristic of the pediatric age, while others occur frequently in adults but rarely in children [15]. The

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Table 1: Registration of very rare tumors to the different European national rare tumor groups and spectrum of tumors evaluated within the EXPeRT initiative.

Selected VRT-Entity	France	Germany	Italy	Poland	U.K.	EXPeRT
nasopharyngeal carcinoma	FRACTURE	NPC	TREP	PPRTSG	NRCT	EXPeRT
salivary gland tumors		STEP				
other ENT tumors						
thyroid cancer		MET				
breast cancer, other breast tumors		STEP				
thymoma						
mesothelioma						
pleuropulmonary blastoma		CWS				
bronchial carcinoma		STEP				
carcinoids, other endocrine cancers		MET				
adrenocortical carcinoma						
pheochromocytoma and paraganglioma						
renal cell carcinoma	SIOP Wilms Study	STEP/SIOP Wilms Study	TREP/AIEOP Wilms Study			
rhabdoid tumors	EpSSG	EURO-Rhabdo CWS/ Wilms/HIT	EpSSG	CWS	EpSSG	
pancreatic tumors, pancreatoblastoma	FRACTURE	STEP	TREP	PPRTSG	NRCT	EXPeRT
gastrointestinal carcinomas						
GIST		CWS				
stromal and ephitelial gonadal tumors	TGM	MAKEI/STEP				
rare mesenchymal tumors	EpSSG	CWS	EpSSG	CWS	EpSSG	
melanoma incl. variants	FRACTURE	STEP	TREP	PPRTSG	NRCT	EXPeRT
other carcinomas						
others						

FRACTURE, groupe FRAnCais des TUmeurs Rares de l'Enfant; TGM, germ cell tumor protocol; TREP, Tumori Rari in Età Pediatrica; STEP, seltene Tumoren in der Pädiatrie; MET, Malignant Endocrine Tumors; NPC, Nasopharyngeal Carcinoma Registry; MAKEI, Malignant Germ Cell Tumor Trial; CWS, Cooperative Soft Tissue Sarcoma Study; HIT, Childhood Brain Tumor Network; PPRTSG, Polish Paediatric Rare Tumours Study Group; NRCT, UK National Registry of Childhood Tumours

latter often seem to be biologically and clinically distinct from their adult counterparts [8, 14]. Since pediatric oncologists may feel themselves unprepared to treat these entities, patients may primarily be seen in the adult cancer specialties. Thus, children may remain outside of the multidisciplinary network established in pediatric oncology centers, lacking access to support services for example, psychosocial and educational support.

During the last decade, several national groups have been founded that specifically focus on VRTs in children and adolescents [16]. These initiatives have increased the awareness of the problem of VRTs. In June 2008 this lead to the formation of a new cooperative group denominated EXPeRT – European Cooperative Study Group for Pediatric Rare Tumors. The main aim of this group is to empower the clinical and biological research on VRT by promoting collaboration between the founder national groups: Italy, France, United Kingdom, Poland and Germany.

In this report we illustrate the present scenario of VRTs in children. We discuss potential problems and future perspectives of the EXPeRT initiative to establish a network that may be able to improve clinical and basic knowledge on pediatric VRTs. Lastly, this article will also serve as an invitation to other national groups to join and collaborate in this international initiative so that children with VRTs may benefit from a closer and stronger network.

Defining the target

In adult oncology, VRTs are a heterogeneous group of entities that is difficult to define. According to the European RARECARE project – an incidence cut-off of less than 6 cases/100 000 population/year should be used to define VRTs [10]. However, this definition would include all childhood cancers. Therefore, it cannot be transferred to pediatric oncology if the aim is to identify those entities for which their rarity poses specific problems.

Considering this dilemma, the Italian TREP project (Tumori Rari in Età Pediatrica [Rare Tumors in Pediatric Age]) introduced a new definition of VRTs, using a lower cut-off, i. e., an annual incidence < 2/millions. Moreover, a specific tumor entity was only included if it was not enrolled in clinical trials, defining it as an orphan disease [7]. This incidence cut-off has to be re-considered when patients up to 20 years are also included [17]. During adolescence, the incidence of some VRTs such as thyroid carcinoma and melanoma increase, up to 5.7 and 6.0 per million per year, respectively (SEER*Stat software version 6.4.4; www.seer.cancer.gov/seerstat).

On the other hand, a purely qualitative definition of childhood VRTs based on histopathologic classification may pose other problems. In the COG initiative, VRTs were generally classified as other malignant epithelial neoplasms and melanomas according to the International Classification of Childhood Cancer subgroup XI of the SEER database [17]. As a consequence, several VRTs such as pleuropulmonary blastoma, pancreatoblastoma or sex cord stromal tumors might be excluded. Therefore, EXPeRT proposes that the group of VRTs should not be defined based on epidemiology or pathology alone. Instead, a VRT is mainly characterized by its status as an orphan disease, thus pointing to the need of the children to have appropriate care.

However, in the different national rare tumor groups, the definition of VRTs, the clinical support and scientific structures may vary significantly [16]. Thus, different entities are included in each national rare tumor projects, while others may be registered to small specific clinical registries and even trials (**Table 1**).

Therefore, a pragmatic definition of a potential EXPeRT cohort of patients was defined that took the specific national aspects into

account: **any solid malignancy or borderline tumor characterized by an annual incidence < 2/million and/or not already considered in clinical trials.** Being a network for pediatric cancers, this definition does not exclude rare adult type cancers that may be suitable for adult trials, if the patients were older. The definition considers both epidemiological and clinical criteria. It focuses the needs of the child with a rare tumor using this definition – thus defining EXPeRT as a cooperative group that primarily focuses on orphan tumors. Moreover, it allows for cooperation with national study groups responsible for specific rare solid tumors. It should be noted that this network does not include rare hematologic malignancies such as rare leukemias or lymphomas, since at least in some European countries, these are enrolled within clinical registries.

Overview on the different European VRT national cooperative groups cooperating in EXPeRT

In most European countries, a cooperative group dedicated to VRT exists, but structures and levels of activities may significantly vary. Nevertheless, the aims of the different national groups are similar:

1) to develop diagnostic and therapeutic recommendations,
2) to collect clinical data on diagnostic work-up, treatment and follow-up,
3) to identify experts "dedicated" to each VRT to give advice to treating clinicians,
4) to establish a collaborative network with other specialists (i.e., adult oncologists, surgeons, endocrinologists, dermatologists) involved in the management of these tumors, and
5) to establish prospective clinical, pathological and biological studies.

The Italian TREP project started in 2000 under the auspices of the Associazione Italiana Ematologia Oncologia Pediatrica, and in cooperation with the Società Italiana Chirurgia Pediatrica [7]. It was born with the dual scope of prompting research and providing all centers with practical patient management schemes and an advisory service. From January 2000 to May 2011, 603 patients < 18 years of age were registered from 38 different Italian centers. TREP was able to register 85% of the 0–14 year-old children with VRTs expected to occur in Italy. In contrast, for adolescents 15–17 year-old the observed/expected ratio was only 19% [18].

The United Kingdom's Children's Cancer & Leukaemia Group founded a Rare Tumour Working Group in 1997 [6]. No dedicated registry was developed, but guidelines were developed and selected (and limited) data were collected throughout the UK National Registry of Childhood Tumours.

In 2006, the German Rare Tumor Working Group was founded as a working group of the German Society of Pediatric Oncology and Hematology [4]. In Germany, there is a long-standing tradition that some VRTs have been registered in prospective studies and registries, respectively (**Table 1**) [5, 11]. For other patients with VRTs, a consultation service has been established [23]. The registration rate is approximately 50 patients per year from institutions in Germany, Austria and Switzerland.

In 2002, the Polish Pediatric Solid Tumors Study Group founded the Polish Pediatric Rare Tumors Study Group [1]. After a first retrospective analysis, an advisory platform was activated and opened for physicians, and new patients were collected prospectively. Treatment recommendations were continuously re-evaluated and improved [25].

The French rare tumor group, named "FRACTURE" (groupe FRAnCais des TUmeurs Rares de l'Enfant) was founded in 2007 on behalf of the French Oncological Pediatric Society and in association with the French national cancer registry [13]. FRACTURE explicitly included the registration not only for malignant VRTs, but also for intermediate malignant and benign tumors that may lead to difficult therapeutic discussions including chemotherapy or radiotherapy. Therapeutic recommendations were developed and distributed to society members [20].

EXPeRT – European Cooperative Study Group for Pediatric Rare Tumors

The main objective of EXPeRT is to promote clinical and biological research in pediatric VRT by intensifying collaboration between the founder national groups and international partners. First, a consensus definition of VRTs has been developed, as described above. Second, urgent scientific questions have been defined for the first international studies. Current initiatives include data exchange based on harmonized data documentation sheets, retrospective and prospective studies of specific tumor entities, and the development of harmonized and internationally recognized guidelines. Lastly, a network for EXPeRT consultation to assist in difficult clinical decisions has been established and standard procedures have been developed. A joint international prospective case registry constitutes an ultimate goal.

The first EXPeRT project focused on analyses of ovarian Sertoli-Leydig cell tumors, pancreatoblastoma and pleuropulmonary blastoma (PPB). The analysis on **pancreatoblastoma** (20 cases collected over a 10 year-period) has been the subject of the first publication [3]. This study illustrates that even at a European level, this tumor is too rare to allow sufficient patient recruitment for prospective clinical trials. Nevertheless, with 20 patients included in this series, it constitutes the largest series published to date. EXPeRT developed a recommendation for a standard approach to pancreatoblastoma, including a standardized diagnostic work-up and a prognostically relevant surgical staging system. Furthermore, multimodal treatment guidelines are proposed that include an initially conservative surgical approach, chemotherapy with PLADO (cisplatin/doxorubicin), post-chemotherapeutic aggressive surgery of both primary tumor and metastases. This strategy has now been integrated into the national groups' recommendations for treatment of VRTs. To substantiate the data, the analysis is currently expanded by retrieval of additional patients both within the EXPeRT members and collaboration partners e.g. from the Scandinavian countries.

In a second project, 42 patients with **ovarian Sertoli-Leydig cell tumors** (SLCT) were analyzed [24]. Again, this study represents the largest pediatric cohort published to date. It illustrates the potentially aggressive nature of these tumors. 10% of patients present with syn- or metachronous bilateral tumors. The analysis showed that in contrast to other sex cord stromal tumors, even intraoperative tumor rupture had a significant impact of prognosis. Moreover, poor histological differentiation was associated with an unfavorable prognosis. A recommendation for diagnostic workup and therapy including cisplatin-based combination chemotherapy was developed.

In a third project, a total of 70 patients with **pleuropulmonary blastoma** (PPB) are currently being evaluated. Interestingly, the

registration rate increased from 0.7 per year in France and UK to 1.4 in Italy where a prospective data collection and national guidelines are available.

In conclusion, these studies demonstrate that international cooperation in VRTs is feasible, and strongly illustrate the benefit of the formation of EXPeRT group. Moreover, these analyses may be a starting point for biological projects on VRTs. In most countries cooperating in EXPeRT, biological specimens are not collected centrally, but a central documentation of collected specimens may exist. Thus, specimens have to be retrieved from many different institutions, an ambitious endeavor which will only succeed if biological research could have a clinical impact. This has been demonstrated for several VRTs such as pleuropulmonary blastomas (DICER1 mutation) [12] or adrenocortical carcinomas (p53 mutations) [22,26], illustrating that biological research on VRTs may significantly contribute to the understanding of their tumor biology. Therefore, biological research on VRTs should ideally be performed within networks such as EXPeRT, through which this data can be correlated to clinical data.

The international scenario

There is only limited information available on other activities dedicated to VRTs outside Europe. These exist mainly in 2 forms: cooperative groups or disease specific registries. In 2002, COG created the rare tumor committee, which included the infrequent tumor subcommittee [17]. The objectives of this subcommittee were to create an organizational framework to facilitate the study of infrequent tumors and develop registries, biospecimen banks, and dedicated clinical trials. However, only 7% of expected patients with melanoma, thyroid carcinoma, nasopharyngeal carcinoma, and adrenocortical carcinomas were eventually registered [17]. In the USA, 4 prospective trials dedicated to VRT have been opened since 2004: 2 for patients with melanoma, 1 for nasopharyngeal carcinoma and 1 for adrenocortical carcinoma, with only moderate patient recruitment.

A different approach has been the creation of disease-orientated registries such as the International Pediatric Adrenocortical Tumor Registry [21], NUT Midline Carcinoma Registry [9] or Pleuro-Pulmonary Blastoma Registry [19]. These initiatives have produced remarkable results especially in the studies of genetic abnormalities and the identification of familial syndromes. However, often they do not provide distinct clinical guidance regarding diagnosis and therapy of these rare tumors.

Last, it should be noted that to our knowledge, there are no comparable initiatives established (or published) in other national or continental groups e.g. in Europe, Asia, Latin America or Africa. If such initiatives were going to be founded, we would encourage colleagues to join international networks such as EXPeRT early.

Future perspectives – reaching beyond EXPeRT?

The data reported by the different national groups clearly illustrate that although the numbers for each clinical entity may be low, the overall number of VRTs is significant. Thus, in each country participating in the EXPeRT initiative, 30–50 VRTs are registered each year. Therefore, VRTs as a clinical group may have a significant impact comparable to that of any other childhood cancers included in prospective studies. The difficulties in conducting prospective trials in an increasingly regulatory environment may adversely affect scientific progress. Nevertheless, improvement of clinical standards for patients that are currently poorly cared for, may have an impact on prognosis, comparable to that achieved in other prospective studies. Therefore, funding of this clinical initiative is urgently required.

To perform research on VRT requires an enormous and prolonged effort, as results may be visible only in the long term. Therefore, motivation of patients and care-givers to participate in VRT networks is crucial for its success. This is a continuous effort of EXPeRT but may only be successful if short-term goals can be achieved such as the harmonization of clinical guidelines. Furthermore, the establishment of clinically helpful consultation networks will foster the motivation of pediatric oncologists to support both national groups and EXPeRT.

In the medium term this collaboration should overcome the mere collection of cases registered in the different countries and further promote prospective trials and biological research. However, prospective randomized trials are virtually impossible. A way to partially overcome the problem of low patient numbers may be the activation of a worldwide collaboration. Such successful networks have already been established for adult rare cancers, e.g. the International Rare Cancer Initiative, joining groups from the U.S., the U.K. and Europe. However, the definition of VRTs in adult oncology is completely different from that in pediatric oncology, with patient numbers that by far exceed those in pediatric oncology. A successful example in pediatric oncology is the International Childhood Liver Tumor Strategy Group – SIOPEL. This group illustrates that an international society such as SIOP may provide the best podium to initiate and continuously support such transcontinental initiatives.

Therefore, EXPeRT is open for collaboration. It wishes to involve additional European countries in the near future. Preliminary discussions between European and North American colleagues are ongoing but structural differences between the different groups should be considered.

An alternative and additional option could be the inclusion of children with VRT in trials open for adults with the same tumors. This approach may be suitable for some entities that primarily arise in adults. However, such concepts disregard the specific characteristics of pediatric VRTs that may have a significantly different biology and clinical behavior compared to their adult counterparts [8]. For instance, pediatric GIST may show poorer response to Imatinib than adult GIST, because they less frequently harbor c-kit mutation [2]. Moreover, a few pediatric patients in an overwhelming population of adults may be of little help both for the trial and the pediatric VRT.

Nevertheless, the regulative authorities now demand that prior to market introduction, new drugs must also be evaluated in pediatric patients, leaving an unsolved dilemma, if the patient numbers are so low. Therefore, phase II trials with new agents have to be promoted, also within the context of EXPeRT. Some studies are underway, specifically focusing on pediatric GIST and pediatric melanoma. These are often coordinated by pharmaceutical companies. Nevertheless, international initiatives such as EXPeRT may contribute with their expertise and the existence of an established network capable to identify suitable patients.

In conclusion, we hope that with EXPeRT, the enormous disadvantage that patients with VRTs may face, will be transformed into an advantage as doctors and scientists recognize that they are forced to collaborate on an international level. Ideally, EXPeRT should facilitate the patients' access to the most up-to-

date diagnosis and treatment. This will hopefully improve the quality of research and clinical care for children that until recently have been partially neglected.

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