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Current Perspective

Defining and listing very rare cancers of paediatric age: consensus of the Joint Action on Rare Cancers in cooperation with the European Cooperative Study Group for Pediatric Rare Tumors

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Abstract Although all tumours are rare in childhood, there are some particularly rare paediatric cancers which have not benefited from advances made by the international paediatric oncology network. To establish a shared definition and produce a list of these entities, the European Union Joint Action on Rare Cancers (JARC) promoted a consensus effort. The definition was based on the incidence rates estimated using the information network on rare cancers (RARECAREnet) database, pooling data from 94 population-based cancer registries and 27 countries. The RARECAREnet list of cancers was used to estimate the incidence rates. This list groups cancers by combining the International Classification of Diseases for Oncology, third edition, morphology and topography codes. According to the consensus, very rare paediatric cancers were identified as those with an annual incidence <2/1000000 and corresponded to 11% of all cancers in patients aged 0–14 years. Two subgroups were identified: tumour types typical of childhood (i.e. hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma) and those typical of adult age (i.e. carcinomas, melanoma). The threshold of 2/1000000 could also be adopted in populations aged 0–19 years: in this case, three tumour types had an incidence rate which was >2/1000000 (i.e. thyroid and testicular cancers and skin melanoma), but the consensus experts considered them as 'very rare' according to their clinical needs (e.g. shortage of knowledge and clinical expertise as the other rare paediatric cancers). The JARC consensus produced a definition and a list of very rare paediatric cancers which may represent a starting point for prioritising research on these tumours, based on data and patients' clinical needs.

1. Introduction

Given the rarity of cancer in childhood [1,2], paediatric oncologists have been developing fruitful national and international cooperation schemes since the 1970s and have, thus, succeeded in improving their patients' survival rates and the quality of the related research [3]. There are some paediatric malignancies, however, that are so seldom observed that they have not benefited from the historical achievements of large-scale paediatric oncology networking [2–5].

In recent years, various schemes have focussed on the challenge of such very rare paediatric cancers [4]. In Europe, national working groups (from Italy, France, the UK, Poland and Germany) [2,4,6–8] came together in 2008 to form the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) [4,9]. The EXPeRT promoted the concept of very rare paediatric cancers as 'orphan diseases', i.e., tumours for which existing data (on their epidemiology, aetiology, molecular biology and clinical history) are scarce, medical expertise is poor, diagnosis is difficult and sometimes delayed, treatment options are rarely supported by solid evidence and research and clinical trials are difficult to conduct [1,2,4]. Following this concept, the EXPeRT chose to promote a pragmatic definition of very rare paediatric cancers, namely those having an annual incidence of <2 per million population up to the age of 18 years, and 'not considered in other trials' [2,4]. This definition aimed to exclude certain entities from the list that had historically benefited from dedicated studies—such as hepatoblastoma or non-rhabdomyosarcoma soft tissue sarcomas [10,11]. Although useful, it was acknowledged that the resulting list was liable to be influenced by the different clinical practices or experience of different cooperative groups.

An incidence cut-off was not defined by the Infrequent Tumor Committee of the North American Children's Oncology Group that stated that very rare tumours are those 'classified as other malignant epithelial neoplasms and melanomas in the International Classification of Childhood Cancer subgroup XI' [12].

The European Commission recently set up a Joint Action on Rare Cancers (JARC), a project aiming to advance quality of care and research on rare cancers in European Union (EU) member states. Under the European Society for Pediatric Oncology guidance, paediatric cancers were included in the project with a specific work package (http://www.jointactionrarecancers.eu/index.php/childhood-cancers). The JARC was, thus, perceived as an appropriate setting for appointing a group of specialists (including EXPeRT members) to promote a consensus effort to re-examine the definition of very rare paediatric tumours.

This article reports the outcome of this group's work and its proposed definition and comprehensive list of very rare paediatric cancers.

2. Methods

The database of the RARECAREnet project (www.rarecarenet.eu) was used to estimate the incidence

rates of cancers in the paediatric population. The RARECAREnet database is drawn from EUROCARE-5, a wider collaborative study on the survival of cancer patients in Europe (www.eurocare.it). An overall 94 European population–based cancer registries (CRs) participating in EUROCARE-5 also joined in the RARECAREnet project: 27 countries contribute to the database (19 covered by national CRs and eight covered by regional CRs partially representing the population of the country). The average European population covered during the period considered (2000–2007) corresponded to 46% of the population of the EU.

The RARECAREnet database suited our purposes because it offers a unique opportunity to obtain incidence data for very rare paediatric cancers.

Incidence rates were estimated for each of the 'tier 1' cancers of the RARECAREnet list, which was generated by a group of multidisciplinary experts after a consultation process promoted by the RARECAREnet project [1]. The purpose of the RARECAREnet list was to identify rare cancers (incidence rate <6/100000) among all malignancies. The RARECAREnet list of cancers is based on their histological classification, i.e., the International Classification of Diseases for Oncology (ICD-O), but the morphological entities it contained needed to be grouped into clinically distinct conditions and then gathered into families of neoplastic diseases. To this end, the experts were asked to group the ICD-O3 morphological entities forming the bottom tier of their list ('tier 3') to obtain a second tier of clinically distinct conditions ('tier 2'), based on their morphology and topography (e.g., 'squamous cell carcinoma of nasal cavity and sinuses', 'soft tissue sarcoma of superficial trunk' and so on), that clinicians would consider clinically relevant. In general, these diagnoses had to correspond to consistent diagnostic and therapeutic approaches. Then, these 'tier 2' entities were clustered into a smaller number of 'tier 1' entities, which also included the not otherwise specified morphologies at any site. 'Tier 1' was intended to include major cancer entities in a clinical sense (e.g., 'epithelial tumours of nasal cavity and sinuses', 'soft tissue sarcoma').

The RARECAREnet list was used for our project because it groups cancers by a combination of morphology and site codes, thereby appropriately capturing the peculiarities of tumours of childhood and adolescence. We calculated the crude incidence rates for 'tier 1' cancers in Europe during the period 2000–2007 in two different but overlapping populations, i.e., patients aged 0–14 years and patients aged 0–19 years at diagnosis.

Eighty-three RARECAREnet CRs providing data for all cancer types were included in the analyses with a 0- to 14-year and 0- to 19-year population of 262,286,367 and 361,139,444, respectively. Eleven anatomical site–specific CRs were excluded from the pool of 94 CRs to avoid any incomplete coverage of some cancers affecting multiple sites, such as neuroendocrine tumours. The population at risk during the period considered was the general population (men and women) in each CR catchment area, expressed as person-years. We ranked the 'tier 1' cancers by declining the incidence rate to identify those with an annual incidence <2 per million population, based on the cut-off previously suggested by the EXPeRT. We also applied higher cut-offs and a lower one (<1). The tumour types selected using the different cut-offs were discussed by a panel of specialists to ascertain whether a cancer considered very rare on the basis of its incidence was actually 'very rare' from the clinical standpoint too.

3. Results

Table 1 shows the incidence rate of the 'tier 1' cancers in the subpopulations of 0- to 14-year-olds and of 0- to 19-year-olds ranked by the declining incidence rate in the 0- to 14-year-olds. These results show that all the childhood cancers perceived by the paediatric oncologists as 'common' in children (lymphomas, acute leukaemias, central nervous system [CNS] tumours, sarcomas, nephroblastoma, neuroblastoma and retinoblastoma) have an annual incidence >2/1000000 (incidence rate bolded in Table 1) and account for the majority (89%) of all childhood cancers.

The remaining 11% of all cancers occurring in this age range represent the group of 'very rare paediatric cancers', which is extremely heterogeneous in terms of tumour types and incidence. Two subgroups can be identified: tumour types typical of adult age (as in most cases) and those typically occurring in children (i.e. hepatoblastoma, pleuropulmonary blastoma and pancreatoblastoma).

Using a lower threshold (<1 per million) excluded extragonadal germ cell tumours, cutaneous melanoma, hepatoblastoma, thyroid carcinoma and non-epithelial tumours of ovary from the very rare tumours list (Table 1). Using cut-offs between 2 and 5 did not substantially change which very rare tumours were listed. A cut-off <6 led to the inclusion of neuroblastoma in the group of very rare paediatric cancers, while higher cut-offs meant including other tumours, such as bone sarcomas (Table 1). Three tumour types with an incidence <2 per million in the 0- to 14-year-olds revealed a higher incidence among 0- to 19-year-olds, i.e., thyroid carcinoma, testicular cancers and skin melanoma; the other histotypes still accounted for 11% of all cancers in 0- to 19-year-olds.

Among the soft tissue sarcomas, rhabdomyosarcoma had an incidence rate of 4.4 and 4 in a million for the groups aged 0–14 years and 0–19 years, respectively. Among bone sarcomas, both of the most common types of cancer in paediatric age had incidence rates >2 in a million, i.e. 2.8 and 3.3 per million in the

Table 1
The number of observed cases and crude incidence rate of RARECAREnet 'tier 1' cancers diagnosed in children (aged 0–14 and 0–19 years at diagnosis) in 83 European cancer registries in the years 2000–2007.

RARECAREnet tier 1 cancer entities	0–14 years			0–19-years		
	Observed cases	Incidence rate	SE	Observed cases	Incidence rate	SE
Lymphoid diseases	12,571	**47.9**	0.4	18,970	**52.5**	0.4
Tumours of central nervous system	3,815	**14.5**	0.2	5,089	**14.1**	0.2
Soft tissue sarcoma	2,248	**8.6**	0.2	3,453	**9.6**	0.2
Acute myeloid leukaemia and related precursor neoplasms	1,842	**7.0**	0.2	2,571	**7.1**	0.1
Nephroblastoma	1,829	**7.0**	0.2	1,953	**5.1**	0.1
Embryonal tumours of central nervous system	1,775	**6.8**	0.2	2,026	**5.6**	0.1
Bone sarcoma	1,731	**6.6**	0.2	3,199	**8.9**	0.2
Neuroblastoma and ganglioneuroblastoma	1,499	**5.7**	0.1	1,513	**4.2**	0.1
Retinoblastoma	856	**3.3**	0.1	856	**2.4**	0.1
Extragonadal germ cell tumours	489	1.9	0.1	702	1.9	0.1
Skin melanoma	348	1.3	0.1	1,619	**4.5**	0.1
Hepatoblastoma	329	1.3	0.1	335	0.9	0.1
Carcinomas of thyroid gland	315	1.2	0.1	1,367	**3.8**	0.1
Non-epithelial tumours of ovary	303	1.2	0.1	666	1.8	0.1
Myeloproliferative neoplasms	268	1.0	0.1	543	1.5	0.1
Neuroendocrine tumours	255	1.0	0.1	707	2.0	0.1
Myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases	228	0.9	0.1	297	0.8	<0.1
Histiocytic and dendritic cell neoplasms	217	0.8	0.1	258	0.7	<0.1
Testicular and paratesticular cancers	210	0.8	0.1	2,016	**5.6**	0.1
Epithelial tumours of skin	146	0.6	<0.1	446	1.2	0.1
Epithelial tumours of major salivary glands and salivary gland–type tumours	114	0.4	<0.1	274	0.8	<0.1
Epithelial tumours of liver and intrahepatic bile tract	91	0.3	<0.1	187	0.5	<0.1
Epithelial tumours of kidney	82	0.3	<0.1	189	0.5	<0.1
Carcinoma of adrenal gland	82	0.3	<0.1	112	0.3	<0.1
Epithelial tumour of lung	28	0.1	<0.1	56	0.2	<0.1
Epithelial tumours of oral cavity and lip	21	0.1	<0.1	54	0.1	<0.1
Epithelial tumours of nasopharynx	17	0.1	<0.1	47	0.1	<0.1
Malignant melanoma of uvea	14	0.1	<0.1	44	0.1	<0.1
Epithelial tumour of colon	13	<0.1	<0.1	92	0.3	<0.1
Olfactory neuroblastoma	13	<0.1	<0.1	20	0.1	<0.1
Epithelial tumours of hypopharynx and larynx	12	<0.1	<0.1	27	0.1	<0.1
Carcinomas of pituitary gland	11	<0.1	<0.1	14	<0.1	<0.1
Epithelial tumours of stomach	10	<0.1	<0.1	58	0.2	<0.1
Adnexal carcinoma of skin	10	<0.1	<0.1	20	0.1	<0.1
Epithelial tumour of ovary and fallopian tube	9	<0.1	<0.1	169	0.5	<0.1
Epithelial tumours of bladder	9	<0.1	<0.1	63	0.2	<0.1
Epithelial tumours of nasal cavity and sinuses	8	<0.1	<0.1	20	0.1	<0.1
Pleuropulmonary blastoma	8	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of pancreas	7	<0.1	<0.1	22	0.1	<0.1
Kaposi sarcoma	7	<0.1	<0.1	19	0.1	<0.1
Pancreatoblastoma	6	<0.1	<0.1	10	<0.1	<0.1
Epithelial tumours of thymus	5	<0.1	<0.1	24	0.1	<0.1
Malignant melanoma of mucosa	5	<0.1	<0.1	6	<0.1	<0.1
Epithelial tumours of oropharynx	4	<0.1	<0.1	11	<0.1	<0.1
Epithelial tumours of rectum	4	<0.1	<0.1	28	0.1	<0.1
Epithelial tumours of pelvis and ureter	4	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of eye and adnexa	3	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of small intestine	2	<0.1	<0.1	12	<0.1	<0.1
Epithelial tumour of trachea	2	<0.1	<0.1	5	<0.1	<0.1
Epithelial tumours of vulva and vagina	2	<0.1	<0.1	5	<0.1	<0.1
Epithelial tumours of prostate	2	<0.1	<0.1	6	<0.1	<0.1
Gastrointestinal stromal sarcoma	2	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of oesophagus	1	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of anal canal	1	<0.1	<0.1	3	<0.1	<0.1
Epithelial tumours of gallbladder and extrahepatic biliary tract	1	<0.1	<0.1	2	<0.1	<0.1
Epithelial tumours of corpus uteri	1	<0.1	<0.1	1	<0.1	<0.1
Epithelial tumours of cervix uteri	1	<0.1	<0.1	40	0.1	<0.1
Trophoblastic tumour of placenta	1	<0.1	<0.1	13	<0.1	<0.1
Malignant mesothelioma	1	<0.1	<0.1	14	<0.1	<0.1
Odontogenic malignant tumours	1	<0.1	<0.1	4	<0.1	<0.1

SE, standard error.
Incidence rates x 1,000,000 with SE. In bold, the incidence rates >2 in a million.

groups aged 0–14 and 0–19 years, respectively, for Ewing sarcoma and 3 and 4 per million, respectively, for osteosarcoma.

Among the tumours in the CNS, embryonal cancers (i.e., medulloblastoma) had an incidence of about 4 in a million for both age groups (0–14 and 0–19 years old); for ependymoma, the incidence rates were 2.6 and 2.3 per million for the 0- to 14-year-olds and 0- to 19-year-olds, respectively and astrocytomas had an incidence rate of about 6 in a million in both age groups (data not shown in the table).

4. Discussion

This expert consensus reports on the definition of very rare paediatric cancers and provides a comprehensive list of these tumours on the strength of epidemiological data. This effort wants to differentiate very rare tumours from other paediatric cancers and might help in suggesting dedicated methodological approaches for research [13]. In fact, although all childhood cancers are rare, designing randomised controlled clinical trials is feasible for most paediatric tumours, thanks to the well-established international cooperative networks, but it is unrealistic for many of the very rare paediatric tumours (it would take years to conclude a clinical trial); for instance, research can certainly be conducted on rhabdomyosarcoma, for which we can roughly estimate that more than 10,000 children have been treated over three decades of (mostly randomised) clinical trials [14], but would be vastly more challenging for pleuropulmonary blastoma or pancreatoblastoma, of which only 65 and 20 cases, respectively, were collected in 10 years at expert centres in Europe [15,16].

The list presented here shows that very rare paediatric cancers include both histotypes typically diagnosed in paediatric age (i.e., hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma) and tumour types that occur frequently in adults (e.g., melanoma, carcinomas). For this second group, collaboration between paediatric oncologists and experienced adult oncologists is essential to enable research; such collaboration may be of critical importance, for example, to make it easier for paediatric patients to access new drugs. Thus, the impact of targeted agents in paediatric patients has not kept pace with the advances seen in adult patients with cancer, with some specific negative experiences recently reported [17,18].

Our study identified the annual incidence threshold of 2 per million as the one distinguishing between the cancer histotypes more and less common in childhood. All cancers with incidence <2 were actually 'very rare' from the clinical standpoint too. This was not true when other cut-offs were used. A lower threshold (<1 in a million) would have excluded some tumour types (thyroid carcinoma and skin melanoma) that are still considered a challenge in paediatric age due to the lack of knowledge and clinical expertise [19,20]. The <2 in a million threshold worked well also for the 0- to 19-year-olds (reflecting the growing attention paid in the last decade to the adolescent population) [21], with three exceptions—thyroid carcinoma, testicular cancer and skin melanoma. These diseases have an annual incidence <2 in a million in children aged 0–14 years and >2 in a million among 0- to 19-year-olds. However, the consensus group considered it important for these entities to be included in the list of very rare paediatric tumours (regardless of their incidence in 0- to 19-year-olds) because these tumours suffer from the same shortage of knowledge and clinical expertise as the other rare paediatric cancers [19,20].

Although the RARECAREnet represents a high-quality data set [22], most of CRs included in this analysis contributed also to the Automated Childhood Cancer Information System [23], the incidence rates based on less than 10 observed cases should be interpreted with caution [24].

In conclusion, the JARC and EXPeRT consensus provides a definition of very rare paediatric cancers founded on the incidence rate of these malignancies in Europe, and it can be useful for paediatric oncologists to prioritise research on these tumours according to their clinical needs and relevance. Noteworthily, the list should be used flexibly and seen as a 'work in progress' because new very rare tumours are coming to light every year, as we learn more about the molecular basis of many cancer types. Just as an example, while CNS tumour groups would exceed the previously defined cut-off, newer and more refined classifications would reveal exceptionally rare entities such as the medulloblastoma SHH p53-mutated variant (with poor prognosis and no consensus on its standard treatment) [25] or the ependymoma YAP1 variant (probably characterised by good prognosis) [26].

Author contributions

A.F. and A.T. drafted the article. A.T. performed the statistical analyses. All authors contributed to data interpretation and report writing and reviewed and approved the final version.

Conflict of interest statement

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

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