Very Rare Tumours in Paediatric Age – From 'Tumori Rari in Età Pediatrica' to the European Cooperative Study Group for Paediatric Rare Tumours

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Abstract

Very rare tumours (VRTs) in paediatric age are a heterogeneous group of cancers very rarely encountered in daily practice, even in large paediatric oncology centres. Some of them are typical of paediatric age, such as pleuropulmonary blastoma or pancreatoblastoma; others are typically found in adulthood, such as carcinomas and melanoma. With the objective of improving the research on, and management of, paediatric VRTs, a national study group was founded and the Tumori Rari in Età Pediatrica (Rare Tumours in Paediatric Age [TREP]) project was launched in Italy in 2000. For the purposes of this project, VRTs have been defined as "any solid malignancy characterized by an annual incidence of <2 cases/million children and not considered in other clinical trials". From January 2000 to December 2011, 652 patients <18 years of age were registered in the TREP database. This article presents the experience gathered so far and underlines the need to develop international collaborations dedicated to paediatric VRTs. With this aim, national groups from Italy, Germany, France, Poland and the UK have created, in June 2008, a new collaborative group named European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT).

Keywords

Very rare tumours, paediatric patients, pleuropulmonary blastoma, nasopharyngeal carcinoma, pancreatic tumours, thyroid carcinoma, melanoma, Tumori Rari in Età Pediatrica (TREP) project, European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT)

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Malignant tumours are relatively uncommon in children, especially considering the incidence of cancer in adults. The difficulty of performing meaningful studies due to the limited numbers of patients treated at each paediatric oncology centre has encouraged oncologists to embark on national and international collaboration schemes in order to perform significant research. The positive results achieved by these schemes seem evident from the gradual improvement in the survival rates in nearly all paediatric tumours, to a point where nearly three in four children diagnosed in developed countries can currently be expected to be 'cured'.

Unfortunately, not all children benefit from these efforts; for those affected by exceptionally rare tumours, the very low incidence of their disease has often limited the interest in research programmes capable of collecting meaningful clinical and biological data. As a consequence, it is extremely difficult to produce evidence-based treatment guidelines for these patients and physicians are forced to treat them on an individual basis.

Paediatric very rare tumours (VRTs) comprise a variety of entities. Some of them are typical of paediatric age, such as pleuropulmonary blastoma or pancreatoblastoma, and are very rarely encountered in daily practice, even in large paediatric oncology centres. Others are typically found in adulthood, such as thyroid carcinoma, colorectal carcinoma, melanoma, thymic tumours and renal carcinoma.

So far, the paediatric oncology community has shown little interest in this group of tumours, which partially explains our lack of understanding of the biology of these disorders and the difficulties encountered in conducting clinical trials. In fact, survival rates have not changed substantially over the years and have remained unsatisfactory for some histotypes. In several European countries, national groups focusing specifically on rare cancers in children have recently been founded to deal with these issues.

The 'Tumori Rari in Età Pediatrica' Project

The Tumori Rari in Età Pediatrica (Rare Tumours in Paediatric Age [TREP]) project was launched in Italy in 2000 and represents a model of network dedicated to rare paediatric tumours. It has not only created a registry for collecting cases, but has also established treatment guidelines for various rare tumours and a network of medical experts who can help clinicians manage their patients.[1]

One of the initial issues faced by the project's team was to define its target. For the purposes of the project, VRTs were defined as "any solid malignancy characterized by an annual incidence of <2 cases/million children and not considered in other clinical trials". The epidemiological cut-off was chosen arbitrarily after an analysis of the tumours identified for inclusion in the project. The second part of the definition underlined the fact that a number of VRTs had not received enough attention from paediatric oncologists, cooperative groups and scientists.

It must be acknowledged that some tumours that we have included in our list of VRTs have an incidence higher than two cases/million children; this is the case of thyroid carcinoma and melanoma, where the incidence increases during adolescence. These tumours have been included in the project because, at the time, they shared the status of 'orphan disease' and the problems of other, less frequent entities. We used the same criteria for rare haematological conditions and central nervous system neoplasms, which were consequently excluded because they came under the remit of other co-operative groups. The list of paediatric VRTs included in the TREP project is given in *Table 1*.

Fifteen different working groups (one for each type of tumour) were gradually formed with a view to developing diagnostic and treatment guidelines. Each working group was co-ordinated by one or two experts, who were also in charge of analysing the data collected, regularly updating the guidelines and advising clinicians on the treatment of children with VRTs. Clinical and treatment data were prospectively collected in a central registry after consent from the patients' families had been received. The possibility of collecting biological samples was also contemplated for some tumours (e.g., adrenocortical carcinoma, pheochromocytoma).

To improve the dissemination of knowledge in Italy, a website (http://trepproject.org) was created to describe the TREP project activities and publish information on different paediatric VRTs.

Number of Patients Included

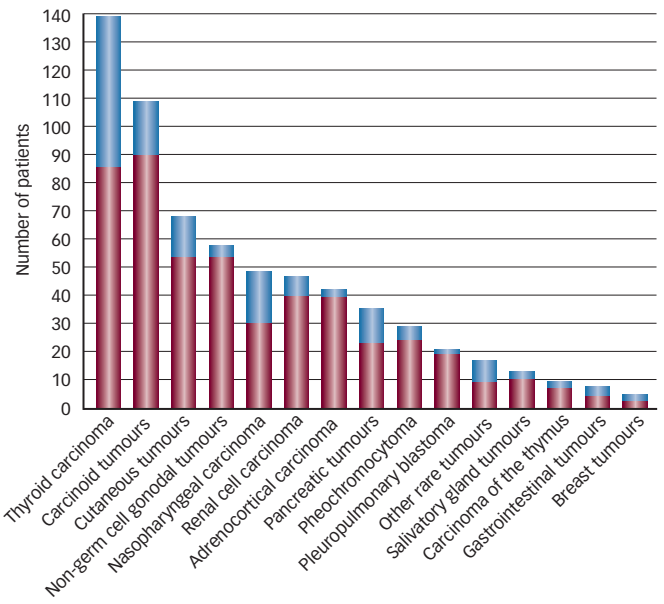
From January 2000 to December 2011, 652 patients <18 years of age were registered in the TREP database by 38 different Italian centres. The median number of patients recruited annually was 54. The most 'common' VRTs were thyroid carcinoma, carcinoid of the appendix, cutaneous tumours and non-germ cell gonadal tumours (see *Figure 1*). Data on an interesting number of exceptionally rare tumours, e.g., carcinoma of the thymus and gastrointestinal tumours, were also prospectively collected.

An analysis performed in collaboration with the Italian Paediatric Haematology/Oncology Association (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP]) epidemiology group showed that the TREP project was able to register 85 % of the cases of VRTs expected to occur in children aged 0–14 years in Italy, judging from incidence data in population-based cancer registries.[2] This figure was similar to those obtained for more common paediatric tumours by other national cooperative groups that started operating much earlier. Unfortunately, the percentage was only 19 % in adolescents (15- to 18-year-olds). Again, the figure was very similar to those seen in other, more common tumours;[3] in a way, it can be seen as more acceptable if one considers that most adolescent patients have adult-type epithelial cancers.

Table 1: Paediatric Very Rare Tumours Included in the 'Tumori Rari in Età Pediatrica' Project

- Nasopharyngeal carcinoma
- Adrenocortical carcinoma
- Pleuropulmonary blastoma (and other lung tumours)
- Carcinoid tumours
- Cutaneous tumours
- Renal cell carcinoma
- Pancreatoblastoma (and other pancreatic tumours)
- Non-germ cell gonadal tumours (ovary/testis)
- Pheochromocytoma and paraganglioma
- Thyroid carcinoma
- Salivary gland tumours
- Breast tumours
- Gastrointestinal tumours
- Carcinoma of the thymus
- Other rare malignant and borderline tumours

Figure 1: Number of Patients Registered in the 'Tumori Rari in Età Pediatrica' Project by Tumour Type



Adolescents (15–18 years) are shown in blue and children (0–14 years) in red.

Lessons Learned

In general, the TREP project has demonstrated that cooperative prospective research on paediatric VRTs is feasible. Merely registering cases would not have been enough, and the success of the project was due to the clinical guidelines and advice provided to all centres taking part and to the involvement of specialists from different disciplines.

For specific types of tumour, various series of cases included in the project were analysed and, despite the limited numbers involved, some key messages were identified.

For some tumours, it was possible to assess the results of multidisciplinary treatments and identify prognostic factors. This was the case, for instance, of pleuropulmonary blastoma: an analysis of 22 patients treated using the multimodal strategy recommended by the TREP guidelines showed estimated 15-year event-free and overall

Table 2: Adult Cancers in Children and Adolescents in the US – Numbers of Cases Registered in the Surveillance Epidemiology and End Results Database (1973–2006)

Type of Cancer	Adults		0–14 years		15–19 years	
	n	Rate	n	Rate	n	Rate
Renal cell carcinoma	98,587	10.49	72	0.03	84	0.10
Hepatocarcinoma	41,605	4.06	101	0.04	86	0.08
Adrenocortical carcinoma	1,097	0.12	59	0.02	18	0.03
Thyroid carcinoma	80,702	8.35	515	0.18	1,485	1.58
Nasopharyngeal carcinoma	7,470	0.85	72	0.02	123	0.14
Malignant melanoma	187,891	20.29	468	0.16	1,368	1.47
Carcinoma of the salivary glands	12,571	1.44	115	0.04	148	0.17
Carcinoma of the colon/rectum	584,427	69.66	31	0.01	143	0.13
Carcinoma of the lung	618,614	71.87	16	0.01	35	0.03
Carcinoma of the thymus	2,414	0.26	11	0.01	13	0.01
Breast carcinoma	752,728	86.04	10	<0.01	55	0.05
Cervical carcinoma	59,125	6.80	8	<0.01	87	0.12
Carcinoma of the bladder	135,399	16.82	9	<0.01	49	0.07
Carcinoma of other sites	1,309,251	149.40	96	0.04	216	0.25
Gastrointestinal stromal tumour	3,484	0.25	9	<0.01	11	0.01
Mesothelioma	10,667	1.18	3	<0.01	8	0.01
Total	4,121,450		3,032		6,457	

The incidence rates shown are per 100,000 population.
Source: modified from Ferrari et al., 2010.[8]

survival rates of 44 % and 49 %, respectively. Performing total resection of the tumour at any time during its treatment resulted in a significantly better prognosis, whereas extrapulmonary involvement at diagnosis coincided with a significantly worse prognosis. On these bases, different risk group were identified and a treatment protocol has been proposed.[4]

Another example is that of nasopharyngeal carcinoma. In a series of 46 paediatric patients prospectively treated over a 10-year period with three courses of cisplatin/5-fluorouracil induction chemotherapy followed by radiotherapy (doses of up to 65 Gy) with concomitant cisplatin, the five-year overall and progression-free survival rates were 80.9 % and 79.3 %, respectively. The only statistically significant prognostic variable was the presence or absence of distant metastases. These findings are consistent with recent reports in the literature, despite the use of lower radiotherapy doses than in adults. They are important considering the need to reduce the overall burden of therapy and severity of long-term sequelae for paediatric patients.[5]

Over an eight-year period, 21 patients <18 years of age with pancreatic tumours were prospectively registered as part of the TREP project, including four with pancreatoblastomas, two with pancreatic carcinomas, three with neoplasms of the endocrine pancreas and 12 with solid pseudopapillary tumours. This series included rather different entities, since pancreatoblastoma is an aggressive embryonic tumour typical of paediatric age while pseudopapillary tumour is a lesion of intermediate malignancy. Overall, the analysis showed that, as in adults, surgery remains the keystone of treatment for pancreatic tumours in paediatric patients. Interesting results were achieved in the four patients with pancreatoblastomas, since three were alive in first remission after a multimodal treatment that included chemotherapy.[6] The analysis confirmed the extreme rarity of these tumours – which makes it impossible to develop prospective studies on a national scale – and the need for international cooperative efforts to tackle their treatment.

For other entities, the prospective registration and follow-up of children enabled us to shed light on some recurrent controversies. This was the case of carcinoid tumour of the appendix, for which the best surgical approach is still a debated matter. Traditionally, right hemicolectomy has been recommended for lesions larger than 2 cm in diameter to reduce the risk of metastasis. A retrospective analysis of 14 cases treated at two institutions belonging to the TREP network prompted us to adopt a more conservative approach.[7] The TREP guidelines were distributed in 2002 and recommended not to perform hemicolectomy whenever the carcinoid tumour was completely resected, irrespective of its size. A close follow-up (every three months for one year after surgery and at increasingly longer intervals thereafter) was recommended, using investigations including 5-hydroxyindoleacetic acid testing, abdominal ultrasound and octreotide scan. An ongoing analysis of more than 100 prospectively registered cases has confirmed that this conservative approach is appropriate and has shown that an intensive follow-up is unnecessary. As a consequence, the TREP guidelines have been amended to reduce the burden of investigations performed after the tumour's resection.

A particular aspect of VRTs in children is that some of them may be relatively common in adults (see *Table 2*). This is the case of all carcinoma types, but also of melanomas and gastrointestinal tumours. Diagnosis and treatment guidelines adopted for children are generally extrapolated from those used to treat adults; however, the clinical and biological characteristics of the diseases may differ in paediatric age. And the more severe long-term consequences of radiotherapy and chemotherapy in children must be taken into account. Taken together, these factors emphasise the need for a tailored therapeutic approach.

Paediatric papillary thyroid carcinoma has a more aggressive onset in children than in adults; approximately 50 % of cases are pluricentric at onset and 70 % extend beyond the thyroid capsule with nodal (70 %) or distant (20 %) metastases. The clinical course of the disease differs from that in adult cases and the outcomes are unaffected by variables known to influence the prognosis in older patients (e.g., low- versus high-risk histological subtype, extrathyroid local invasion, nodal or distant metastases, recurrence and type of surgery). This is due mainly to the fact that thyroid-stimulating hormone (TSH) suppression therapy (L-thyroxine) is extremely effective in controlling tumour growth and survival approaches 100 %. The difference between paediatric and adult disease is also supported by biological and genetic findings: paediatric papillary subtypes are often characterised by the *RET/PCR3* translocation (not seen in adult cases), while they lack the *BRAF* involvement typical of adult disease.[8]

Approximately 2 % of all cases of melanoma occur in patients under 20 years of age, but only an exceedingly small minority of these develop in prepubertal children. The clinical features of childhood melanoma may feature a nodular, pedunculated or amelanotic lesion, sometimes simulating a pyogenic granuloma. The ABCDE (asymmetry–border irregularity–colour variability–dimension over 6 mm–evolution) clinical rule commonly adopted in adults may consequently be useless and even misleading in cases of childhood melanoma. The biological characteristics of paediatric melanoma

partially coincide with those of adult melanoma – for instance, *BRAF* oncogene activation and frequent loss of the *CDKN2A* gene have been reported – but other traits have been found that seem to be peculiar to the younger age group (frequent *c-Kit* gene alterations), hinting at the involvement of novel genetic networks. Most of the clinical information on paediatric melanoma comes from retrospective reports, and treatment strategies have generally been extrapolated from experience with adults. In various series, authors reported thicker lesions and more advanced stages at diagnosis, but also the impression that melanoma may behave better in younger patients.[8]

Although experience with thyroid papillary carcinoma and melanoma seems to indicate that these tumours tend to behave less aggressively in children than in adults, this is not true of all adult tumours occurring in paediatric age. For instance, carcinoma of the thymus shares the same dismal prognosis in adults and in children, and effective chemotherapy regimens are yet to be identified.[9]

In the case of colorectal carcinoma, the prognosis is even worse when the tumour occurs in paediatric age. This has been explained by a higher incidence of unfavourable aggressive histotypes and an advanced clinical stage at onset. Reported survival estimates at five years were 40 % for children and adolescents and 60 % for adults.[8]

All these findings show that the TREP project was able to collect prospective data and, in many cases, provide homogeneous treatment for a significant number of children with VRTs in Italy. On the other hand, it has become clear that the number of patients who could be enrolled within a reasonable time period in a national-scale protocol would never be sufficient to conduct randomised clinical trials designed to answer specific therapeutic questions.

Hereditary Cancer Syndromes

The development in a child of a tumour typically seen in adults may lie on the left edge of a Gaussian distribution curve of a relatively frequent adult cancer, or it may be the sign of a more complex situation. It is now clear that there may be a relatively higher proportion of hereditary cancer syndromes among young patients with VRTs, and a VRT in a child may be the hallmark of one of these syndromes. Pheochromocytoma is a typical example, as it may be associated with alterations of the von Hippel–Lindau *(VHL)* gene, of the genes encoding the subunits B and D of succinate dehydrogenase, of the *RET* proto-oncogene predisposing to multiple endocrine neoplasia type 2, or of the neurofibromatosis type 1 gene. A germ line mutation typical of one of these hereditary conditions has been identified in up to 59 % of apparently sporadic pheochromocytomas found in patients aged up to 18 years, and in 70 % of those detected in patients aged up to 10 years.[10] Based on the TREP guidelines, 17 patients with pheochromocytoma were screened and genetic anomalies were found in 10 of them, confirming that sporadic pheochromocytoma may be the first sign of a hereditary syndrome and that genetic screening is appropriate in order to provide counselling for the families affected.

The TREP project also investigated a possible association between renal cell carcinoma and *VHL* mutations, because the latter occur in adults with clear cell renal carcinoma. None of the 13 patients analysed was found positive for *VHL* mutations, suggesting that any such association would be a very rare event.

Table 3: Examples of Hereditary Cancer Syndromes Known to Be Associated with Rare Paediatric Tumours

	Affected Gene	Syndrome
Adrenocortical carcinoma	*p53* mutation	Li–Fraumeni syndrome
Pheochromocytoma	*VHL* gene, *RET* proto-oncogene	*VHL* syndrome, MEN2 syndrome
Colorectal carcinoma	*APC* gene	Familial adenomatous polyposis
Pleuropulmonary blastoma	*DICER1*	*DICER1* syndrome
Ovarian Sertoli cell tumour	*DICER1*	*DICER1* syndrome
Testicular Sertoli cell tumour	*PRKAR1A*	Carney complex

APC = adenomatous polyposis coli; MEN2 = multiple endocrine neoplasia type 2; VHL = von Hippel–Lindau.

Other VRTs have been found to be associated with hereditary genetic syndromes, such as adrenocortical carcinoma with Li–Fraumeni syndrome or pleuropulmonary blastoma with the recently described *DICER1* syndrome (see *Table 3*). It therefore seems appropriate to recommend systematically searching for genetic alterations in all children diagnosed with a VRT.

New Entities

Pathologists and biologists are continually identifying new malignant neoplasms or variants of more classical lesions. This process may be accelerated in the near future thanks to the availability of more modern tools which, by using new immunohistochemical markers and searching for new genetic abnormalities, will enhance our diagnostic capacity. Paediatric oncologists are expected to increasingly encounter new entities, such as nuclear protein in testis (NUT) carcinoma, myoepithelial carcinoma or rare subtypes of soft tissue sarcomas. The recognition and treatment of such patients poses a real challenge for paediatric oncologists and it may take many years in order to gain at least a general idea of how to establish a diagnosis and how to treat the children concerned.

An international network dedicated to VRTs should be able to take in charge these 'new tumours' as promptly as possible, reducing the time gap between the first description of a tumour and the formulation of guidelines or treatment protocols.

From 'Tumori Rari in Età Pediatrica' to the European Cooperative Study Group for Paediatric Rare Tumours

The need to develop projects dedicated to paediatric VRTs has been recognised in other countries too. In the UK, the Children's Cancer and Leukaemia Group founded a Rare Tumour Working Group in 1997. Since then, guidelines on endocrine tumours have been prepared, but no attempts have been made to register patients prospectively, so the group relies mainly on information collected in a national registry.

Between 2002 and 2006, national groups were founded in other European countries, with goals similar to those of the TREP group: the Seltene Tumoren in der Pädiatrie (Rare tumours in paediatrics) working group in Germany, the Polish Paediatric Rare Tumours Study Group in Poland and the Groupe Français des Tumeurs Rares de l'Enfant (French group for rare tumours in children) in France. Albeit featuring rather different organisation modes and activity levels, these groups all share the idea that multinational cooperation is needed to improve our knowledge of paediatric VRTs as well as outcomes for children. This led, in June 2008, to the foundation of a new

collaborative group called the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT). The EXPeRT's main aim is to empower research on paediatric VRTs by promoting cooperative schemes between its founding national groups – i.e., from Italy, France, the UK, Poland and Germany.

As a first step, the EXPeRT decided to combine data collected by each national group on certain tumours included in the list of paediatric VRTs. A harmonised core data sheet for the standardised documentation of clinical data of children with rare cancers was developed, and this data sheet was subsequently adapted for three retrospective studies focusing on ovarian Sertoli–Leydig cell tumours, pancreatoblastoma and pleuropulmonary blastoma.

Pancreatoblastoma was selected as the first tumour type to be analysed and was the subject of a publication in 2011.[11] Over a 10-year period, only 20 cases had been collected in the EXPeRT countries, suggesting that, even at European level, this disease is too rare to enable the recruitment of a sufficient number of cases to conduct clinical trials leading to evidence-based treatment guidelines. The EXPeRT group has nonetheless been able to propose a standardised approach to pancreatoblastoma including a surgical staging system, an initial conservative surgical approach, chemotherapy according to the PLADO (cisplatin and doxorubicin) regimen and aggressive surgery after chemotherapy on both primary tumour and any metastases.[11]

We expect that this positive experience will strengthen the collaboration between the countries involved in the EXPeRT and stimulate the formation of similar groups in other European countries. In addition, collaboration with already existing disease-oriented registries and collaborative groups will be actively sought, as worldwide initiatives are necessary. This will hopefully improve the quality of research and the outcomes of treatment for children who have, until recently, been rather neglected. ■

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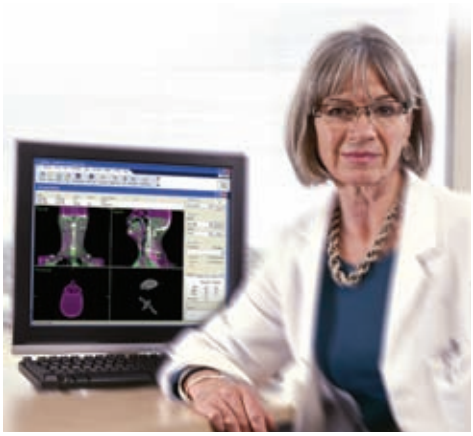

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