



HAL
open science

The French FRACTURE database: A way to improve knowledge on management of children with very rare tumors

Coralie Mallebranche, Yves Reguerre, Brice Fresneau, Nicolas Andre, Claire Berger, Claire Briandet, Marie-pierre Castex, Anne-sophie Defachelles, Cécile Faure-Conte, Julien Lejeune, et al.

► To cite this version:

Coralie Mallebranche, Yves Reguerre, Brice Fresneau, Nicolas Andre, Claire Berger, et al.. The French FRACTURE database: A way to improve knowledge on management of children with very rare tumors. *Pediatric Blood and Cancer*, 2022, 69 (12), pp.e30003. 10.1002/pbc.30003 . hal-04030742

HAL Id: hal-04030742

<https://hal.science/hal-04030742>

Submitted on 24 May 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

The French FRACTURE database: A way to improve knowledge on management of children with very rare tumors

Coralie Mallebranche¹ | Yves Reguerre² | Brice Fresneau³ | Nicolas Andre⁴ |
 Claire Berger⁵ | Claire Briandet⁶ | Marie-Pierre Castex⁷ | Anne-Sophie Defachelles⁸ |
 Cécile Faure-Contier⁹ | Julien Lejeune¹⁰ | Sébastien Klein¹¹ | Guy Leverger¹² |
 Aude Marie-Cardine¹³ | Caroline Oudot¹⁴ | Claire Freycon¹⁵ | Stéphanie Proust¹ |
 Marianne Roumy¹⁶ | Estelle Thebaud¹⁷ | Cécile Verite¹⁸ | Brigitte Lacour^{19,20} |
 Daniel Orbach²¹

¹Pediatric Immuno-Hemato-Oncology Unit, CHU Angers, Angers, France

²Pediatric Oncology and Hematology Unit, CHU Saint Denis de la Réunion, Bellepierre, France

³Department of Child and Adolescent Cancer, Gustave Roussy Institute, Villejuif, France

⁴Pediatric Oncology, La Timone Hospital, Marseille, France

⁵Lyon University, Jean Monnet University, INSERM, U1059, Sainbiose, University Hospital, Pediatric Hematology-Oncology Department, Saint-Etienne, France

⁶Pediatric Oncology, CHU Dijon-Bourgogne, Dijon, France

⁷Hematology, Immunology and Oncology, Children's Hospital, Toulouse, France

⁸Pediatric Oncology Unit, CLCC Oscar Lambret, Lille, France

⁹Pediatric Oncology, Institute of Pediatric Hematology and Oncology (IHOPE), Lyon, France

¹⁰Pediatric Oncology and Hematology, CHRU Tours, Tours, France

¹¹Pediatric Oncology and Hematology, CHU Jean-Minjoz, Besançon, France

¹²Hemato-Immuno-Oncology, Trousseau Hospital, APHP, Paris, France

¹³Pediatric Hemato-oncology, CHU Rouen - Child Hospital, Rouen, France

¹⁴Pediatric Oncology, CHU Limoges, Limoges, France

¹⁵Pediatric Onco-Hematology, CHU Grenoble - Hôpital Couple-Enfant, La Tronche, France

¹⁶Pediatric Clinical Research Platform, CHU Angers, Angers, France

¹⁷Pediatric Immuno-Hemato-Oncology Unit, CHU Nantes, Nantes, France

¹⁸Pediatric Hematology and Oncology, CHU Bordeaux, Bordeaux, France

¹⁹French National Registry of Childhood Solid Tumors, CHU Nancy, Nancy, France

²⁰Inserm UMR 1153, Centre of Research in Epidemiology and Statistics (CRESS), Paris University, Epidemiology of Childhood and Adolescent Cancers Team (EPICEA), Paris, France

²¹SIREDO Oncology Centre (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, PSL University, Paris, France

Abbreviations: ACC, adrenocortical carcinoma; ACT, adrenocortical tumors; CDDP, cisplatin; CR, complete remission; CT, chemotherapy; EXPERT, European Cooperative Study Group for Pediatric Rare Tumors; FRACTURE, French Very Rare Tumors Committee; NET, neuroendocrine tumor; PARTNER, PAediatric Rare Tumours Network - European Registry; PD, progressive disease; PMSI, Information System Medicalisation Programme (*programme de médicalisation des systèmes d'information*); PPB, pleuropulmonary blastoma; RNCE, French National Pediatric Tumor Registry (*Registre National des Cancers de l'Enfant*); SFCE, French Society of Pediatric Oncology (*Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent*); SPPP, solid pseudopapillary neoplasms of the pancreas; STEP, German Pediatric Rare Tumor Group; TREP project, Italian Project on Rare Pediatric Tumors; UCNT, undifferentiated nasopharyngeal carcinoma; VRTs, very rare tumors.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Pediatric Blood & Cancer* published by Wiley Periodicals LLC.

Correspondence

Coralie Mallebranche, Pediatric
Immuno-Hemato-Oncology Unit, CHU Angers,
Angers, France.

Email: coralie.mallebranche@chu-angers.fr

Abstract

Introduction: Very rare pediatric tumors (VRTs), defined by an annual incidence ≤ 2 per million inhabitants, represent a heterogeneous group of cancers. Due to their extremely low incidence, knowledge on these tumors is scant. Since 2012, the French Very Rare Tumors Committee (FRACTURE) database has recorded clinical data about VRTs in France. This study aims: (a) to describe the tumors registered in the FRACTURE database; and (b) to compare these data with those registered in the French National Registry of Childhood Cancer (RNCE).

Methods: Data recorded in the FRACTURE database between January 1, 2012 and December 31, 2018 were analyzed. In addition, these data were compared with those of the RNCE database between 2012 and 2015 to evaluate the completeness of the documentation and understand any discrepancies.

Results: A total of 477 patients with VRTs were registered in the FRACTURE database, representing 97 histological types. Of the 14 most common tumors registered in the RNCE (772 patients), only 19% were also registered in the FRACTURE database. Total 39% of children and adolescent VRTs registered in the RNCE and/or FRACTURE database (323 of a total of 828 patients) were not treated in or linked to a specialized pediatric oncology unit.

Conclusion: VRTs represent many different heterogenous entities, which nevertheless account for 10% of all pediatric cancers diagnosed each year. Sustainability in the collection of these rare tumor cases is therefore important, and a regular systematic collaboration between the FRACTURE database and the RNCE register helps to provide a more exhaustive picture of these VRTs and allow research completeness for some peculiar groups of patients.

KEYWORDS

childhood malignancies, FRACTURE database, national registry, very rare tumors

About 2200 new cases of child and adolescent cancers are diagnosed every year in France. They are systematically registered in the French National Registry of Childhood Cancer (*Registre National des Cancers de l'Enfant* - RNCE).¹ Overall, 8%–10% of these malignancies are considered “very rare tumors” (VRTs), with an annual incidence of less than two per million inhabitants.² VRTs in children and adolescents represent a heterogeneous group of cancers. Due to their extremely low incidence, knowledge on these tumors is scant and they are the subject of only very few prospective studies; for example, a nasopharyngeal carcinoma study in Germany.³ Consequently, therapeutic recommendations are difficult to produce, and physicians have to treat VRTs on an individual basis with weak evidence-based medicine support.⁴ In order to face these difficulties, over the foregoing years, the European Pediatric Oncology Community has developed projects specifically dedicated to VRTs.⁵ The main types of tumors anticipated were undifferentiated nasopharyngeal carcinoma (UCNT), solid pseudopapillary neoplasms of the pancreas (SPPP), pleuropulmonary blastoma (PPB), carcinoid tumor, pheochromocytoma/paraganglioma, adrenocortical tumors (ACT), thyroid carcinoma, and cutaneous melanoma. Some VRTs such as PPB arise exclusively in pediatric patients, while other

tumors develop generally during adulthood but are rarely seen in children and adolescents (i.e., colon cancer and malignant melanoma). These rare malignant tumors are less known to pediatricians and even pediatric oncologists. However, in recent years, the European EXPERT group (European Cooperative Study Group for Pediatric Rare Tumors) published some specific recommendations to help clinicians in treating patients with these rare entities.^{5–12} The PARTNER (PAediatric Rare Tumours Network - European Registry) project aims to extend knowledge of these rare diseases and to build a single European registry that links the existing national registries dedicated to children and adolescents (0–18 years) with VRTs. European countries, where no VRT registry exists, should register their patients directly in this new European registry.⁵ In France, the Very Rare Tumor Committee (FRACTURE) of the *Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent* (French Society of Pediatric Oncology - SFCE) was founded in 2007 with several objectives.⁵ Its main aim was to record as many childhood and adolescent cases of VRTs as possible on a national scale, using the FRACTURE database, a national collection database open since 2012. The purpose of the database was to facilitate analysis of these rare diseases, mainly in

order to develop harmonized dedicated guidelines for diagnosis, treatment, and follow-up.^{13–16} The number and heterogeneity of these pathologies, the variety of their age of onset, and the various sites of care (surgery, oncology, dermatology, ophthalmology, endocrinology, etc.) make it difficult to systematically register these patients. To date, very few countries have reported data from their national database or experience with rare pediatric tumors (Germany, Italy, Brazil). Here, we present the French experience, which represents one of the oldest and largest databases.

The main objective of this article is to describe the cases of VRTs registered in the FRACTURE database and to perform a detailed analysis for the most common entities, describing their treatments and outcomes. The secondary objective is to compare these data with those registered in the French RNCE to analyze the rate of effective registration in the dedicated VRT database and to explore the reasons of discrepancies.

1 | MATERIALS AND METHODS

This retrospective study analyzed all data recorded in the FRACTURE database between 2012 and 2018 and compared them to data available in the RNCE during a 4-year period (2012–2015). The FRACTURE database is a prospective voluntary repository that since 2012 has collected clinical, biological, and therapeutic information on patients from 0 to 18 years old treated in one of the 32 SFCE centers for very rare malignant and borderline tumors. The inclusion criterion was a very rare malignant tumor or a very rare tumor of intermediate malignancy occurring in a person younger than 18 years old. VRTs were described as tumors with an annual incidence of less than two cases per million inhabitants, as defined by Ferrari et al.² Central nervous system tumors and hematological malignancies were excluded, as were other tumors within the field of another SFCE working group or registered in a specific clinical trial: rhabdoid tumors, hepatoblastoma, retinoblastoma, malignant germ cell tumors, and rare histotypes of soft part sarcomas. The purpose of the FRACTURE database is not to provide extensive epidemiological analysis, as the voluntary nature of the report was not expected to ensure its completeness. The informed consent of the family and/or the patient is collected in each center by the clinician. Data are anonymously collected in a secured electronic database (EnnovClinical software) housed in the Angers University Hospital. Authorization from the National Commission for Data Protection and Liberties (CNIL-France) was obtained in October 2011. At regular points, a clinical update is performed to collect the last follow-up information. The validation of the data is carried out by the clinical research staff of the University Hospital of Angers. For this study, data were extracted on January 31, 2019, with an update on December 31, 2021.

All data were analyzed using descriptive statistical methods. Tumor failure was defined as relapsed disease, progressive disease (PD), or death. Locoregional relapse was defined as recurrence at the primary thoracic site or in directly adjacent thoracic tissues, and metastatic relapse was defined as appearance of tumors at distant sites. Survival

time was calculated from the date of diagnosis (initial biopsy/surgery) to the time of last follow-up or event. Overall survival was calculated by the Kaplan–Meyer method. R software (version 3.5.1) and R packages wordcloud2 (version 0.2.1) and ggplot2 (version 3.0.0) were used to create the figures.

The RNCE is a population-based registry that ensures an exhaustive retrospective collection of all cancer cases in children under 18 years of age in mainland France and four overseas departments.^{17,18} Based on the previous French RNCE data, the initial annual expected number of VRT cases was between 150 and 200. The main source of collection is active research by trained investigators of pediatric hematology and oncology departments in France. Active registration is supplemented by an annual request for claim data from the Information System Medicalisation Programme (PMSI) of University Hospitals (CHU) and Cancer Centers, which lists all children aged less than 15 years who have been admitted to any department with a diagnosis of cancer or a brain tumor, including a few borderline diagnoses. This source of information enables identification of children with cancer treated in departments other than pediatric oncology departments. Systematically recorded data include child characteristics, information on cancer diagnosis and patients' pathway from diagnosis to treatment, initial treatment, vital status, and last contact date. The RNCE produces incidence and survival estimates on a national scale.¹⁹ The RNCE is evaluated by the Registry Evaluation Committee, which certifies the quality and completeness of the collected data. At the time of the analysis, RNCE data were exhaustive up to 2015, so the selected period for the comparison with the FRACTURE database was 2012–2015. This comparison was made on August 31, 2019. Moreover, as some VRTs are actually nonmalignant tumors, we widened the selection of the RNCE to include borderline tumors that are also recorded in the registry but not included in the incidence figures. Databases were combined using patients' initials, date of birth, date of diagnosis, and type of tumor. Pediatric VRTs represent a very heterogeneous group of tumors, with difficult classifications for some entities. To simplify the comparative analysis complicated by this great heterogeneity, we decided to consider for analysis only tumors for which more than 15 cases were reported (RNCE alone, FRACTURE alone, or in both) over the period 2012–2015.

For the classification of patient treatment sites, the term “specialized pediatric oncology unit” corresponds to pediatric oncology units in university hospitals and pediatric oncology units in cancer centers.

2 | RESULTS

2.1 | Description of the FRACTURE database

Overall, 477 patients fulfilling the inclusion criteria were included in the FRACTURE database, accounting for 97 different tumor histological types (Figure 1, Table 1) over a period of 7 years (January 1, 2012 to December 31, 2018). Total 258 patients were female (58%) and 185 were male (42%) (unknown: 34 cases). The median age of patients at diagnosis was 12 years (range: 0.0–18.9). Many different entities were

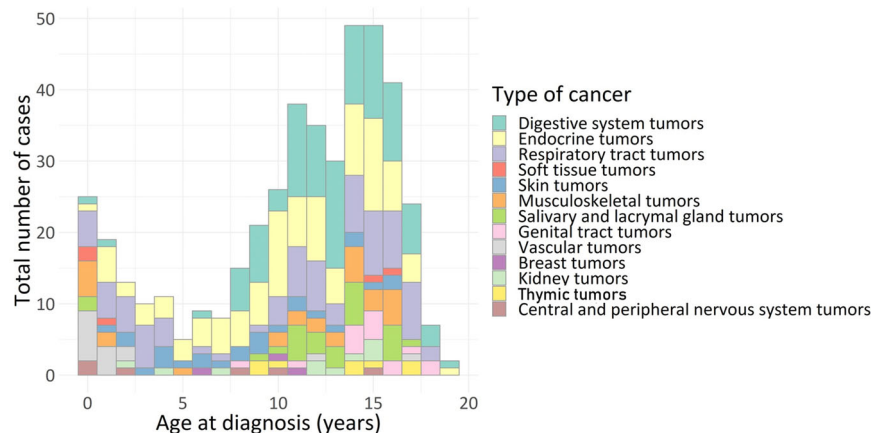


FIGURE 1 Distribution by age at diagnosis and type of very rare tumors recorded in the FRACTURE database between 2012 and 2018

included, regardless of the age of the patient. Two peaks of occurrence are present: before the age of 3, and after the age of 10 years (Figure 1).

2.2 | Clinical characteristics of the most frequent tumors registered in the FRACTURE database

2.2.1 | Neuroendocrine tumors ($n = 66$)

The appendix was the most common location of pediatric neuroendocrine tumors (NET) (54 cases) (Table 2). All tumors were diagnosed at a localized stage, and 39 patients had a tumor of less than 20 mm. Treatment consisted of tumor resection alone in 40 patients, which was always macroscopically complete (unknown: 11 cases). A second surgery was necessary for three patients after initial incomplete surgery. One of them was in complete response after a right hemicolectomy, performed following analysis of histological criteria. Overall, 37 patients were in complete remission at the end of treatment (unknown: 17 cases). After a median follow-up of 8 months (range: 0–141), all patients were alive without any recurrence. Overall survival at 5 years was 100% (unknown: 12 cases).

NETs involved another site for 12 patients: nine in lung (median follow-up 60 months, range: 9.9–87.9, eight in first complete remission, one alive with disease), two in pancreas (one patient died of disease 24 months of evolution; unknown: one case), and one in the liver (alive without disease after 59 months of follow-up).

2.2.2 | Solid pseudopapillary neoplasms of the pancreas ($n = 35$)

Among the 35 patients, almost all were diagnosed at a localized stage (and one patient had regional nodal involvement N1). Treatment was exclusive surgery for all patients, with complete remission for 31 patients (four unknown). After a median follow-up of 19 months (range: 0.5–129), all patients were alive without disease and one had a PD (unknown: five cases). Overall survival at 5 years was 100% (unknown: five cases).

2.2.3 | Pleuropulmonary blastoma ($n = 25$)

Among the 25 patients with PPB, seven had pleural involvement (unknown: one case). Metastatic disease was present in three patients (bone in two cases, contralateral lung in one case). Almost all patients for whom the data were available had an initial surgery (18 R0 [complete histologic] resection, three biopsy, unknown: four cases) and received chemotherapy (18 chemotherapy; unknown: six cases). Complete remission was achieved for 24 patients (one PD). After a median follow-up of 51 months (range: 3–110), two patients died of disease and 23 were alive. Overall survival at 5 years was 89% (unknown: four cases).

2.2.4 | Pheochromocytoma ($n = 21$) and paraganglioma ($n = 13$)

Among the 21 patients with pheochromocytoma, one had a bilateral disease, one a lymph node involvement, and two had metastasis (lung and bone metastasis: one each). Twenty patients underwent an initial surgical resection (one biopsy alone), resulting in microscopic complete resection for 17 patients (85%). No patients received chemotherapy or radiotherapy. One patient (with bone metastases) received MIBG therapy.

At the end of the treatment, complete remission was achieved for 20 patients (one partial remission). All patients were alive at the last follow-up (median follow-up: 42 months; range: 1–107) including one patient in third complete remission and another alive with disease (unknown: three cases). Overall survival at 5 years was 100% (unknown: three cases).

Among the 13 patients with paraganglioma, none had lymph node involvement (unknown: three cases) or metastatic disease at diagnosis (unknown: two cases). Nine patients underwent complete resection surgery at diagnosis, one a biopsy followed by complete resection, and one a delayed surgery. One patient did not undergo any surgical procedure (unknown: one case). One patient had multiple paragangliomas; he underwent complete resection of three lesions (one coeliomesenteric lesion and two carotid lesions), and irradiation with proton therapy of a tympano-jugular lesion not accessible to surgery. No other

TABLE 1 Number of cases included in the very rare tumor FRACTURE database for each tumor type between 2012 and 2018

Histotypes	Number of cases
Neuroendocrine tumors:	66
Appendiceal	54
Lung	9
Pancreas	2
Liver	1
Thyroid carcinoma	52
Papillary thyroid carcinoma	39
Follicular thyroid carcinoma	9
Medullary thyroid carcinoma	4
Nasopharyngeal carcinoma	44
UCNT	43
Nasopharyngeal papillary carcinoma	1
Pancreatic tumors	38
Solid pseudopapillary neoplasm	35
Acinar cell carcinoma	1
Pancreatoblastoma	1
Undifferentiated carcinoma	1
Pulmonary and pleural tumors	35
Pleuropulmonary blastoma	25
Mucoepidermoid carcinoma	3
NUT carcinoma	3
Adenocarcinoma	1
Epidermoid carcinoma	1
Mesothelioma	1
Pulmonary chondroid hamartoma	1
Pheochromocytoma/paraganglioma	34
Pheochromocytoma	21
Paraganglioma	13
Cutaneous tumors	28
Melanoma	26
Basal cell carcinoma	1
Solitary cutaneous mastocytoma	1
Adrenocortical tumor	27
Salivary glands tumor	27
Mucoepidermoid carcinoma	14
Acinar cell carcinomas	7
Undifferentiated carcinoma	2
Mammary analog secretory carcinoma	1
Salivary gland analog tumor	1
Adenoid cystic carcinoma	1
Sialoblastoma	1
Hemangioendothelioma	14
Ovarian non-germ cell tumor	13
Mucinous cystadenoma	5
Carcinoma	2
Adenocarcinoma	2
Serous cystadenoma	2
Sclerosing stromal tumor	1
Steroid cells tumor	1
Gastrointestinal carcinoma	12
Kidney tumors	10
Giant cells tumors	9
Thymic tumors	8

(Continues)

TABLE 1 (Continued)

Histotypes	Number of cases
Gastrointestinal stromal tumor	5
Others rare tumors	55
Total	477

Abbreviations: FRACTURE, French Very Rare Tumors Committee; UCNT, undifferentiated nasopharyngeal carcinoma.

patient received radiotherapy (unknown: one case) or chemotherapy (unknown: one case). All patients were in complete remission at the last follow-up (median follow-up: 34 months, range: 1–54) (unknown: two cases). Overall survival at 5 years was 100% (unknown: two cases).

2.2.5 | Papillary thyroid carcinoma (n = 39)

Among the 39 patients with a papillary thyroid carcinoma, 16 had regional nodal extension (unknown: 17 cases) and 12 metastatic diseases mostly located in the lung (eight patients; unknown: six cases). Carcinoma diagnosis was made after thyroid biopsy for six patients or surgical resection for 29 patients (unknown: four cases). Treatment with iodine-131 was undertaken in 30 patients. No patients received external radiotherapy. After a median follow-up of 25 months (range: 3–124), all patients are alive with six patients having residual disease and one in second complete remission (unknown: eight cases). Overall survival at 5 years was 100% (unknown: eight cases).

2.2.6 | Adrenocortical carcinoma (n = 25)

Among the 25 patients with adrenocortical carcinoma (ACC), four patients had metastasis (two in lung and two in peritoneum due to a tumor rupture). Postsurgical treatment comprised chemotherapy (etoposide–cisplatin–doxorubicin) and mitotane for seven patients with stage III and IV ACC. One patient with stage I carcinoma received only mitotane, and one patient received only chemotherapy. Two patients presented an early death, one by toxicity and one during surgery. After a median follow-up of 19 months (range: 0–192), six patients died, two during initial treatment and four by disease after relapse or progression and 17 were alive (unknown: two cases). Overall survival at 5 years was 65% (unknown: three cases).

2.2.7 | Undifferentiated nasopharyngeal carcinoma (n = 43)

Among the 43 patients with UCNT included in the FRACTURE database, only one patient had lung metastasis at diagnosis. All patients received chemotherapy (unknown: five cases), 34 with 5-fluorouracile (5-FU)-based regimens, including 27 with 5-FU and cisplatin (CDDP). All patients received radiotherapy (unknown: eight cases) and 25 received maintenance β -interferon (unknown: 10 cases).

TABLE 2 Characteristics of patients with the most frequent tumors in the FRACTURE database between 2012 and 2018

	NET of appendix	SPPP	PPB	Pheochromocytoma	Paraganglioma	Papillary thyroid carcinoma	ACC	UCNT	Cutaneous melanoma
Number of cases	54	35	25	21	13	39	25	43	26
Median age (years)	12.5 [6.4; 17.6]	12.4 [7.0; 17.2]	2.2 [0.2; 4.2]	10.3 [6.8; 15.1]	14.1 [8.6; 18.0]	12.8 [4.2; 17.5]	4.7 [0.4; 15.4]	13.7 [8.5; 18.2]	8.9 [1.1; 15.5]
Staging									
Locoregional	Localized: 54	N0: 27 N1: 1 NS: 7	NS	N0: 20 N1: 1 Bilateral: 1	N0: 9 NS: 4	N0: 6 N1: 16 NS: 17	NS	8th TNM staging: Stage II: 1 Stage III: 7 Stage IVa: 12 NS: 12	N1: 7
Metastasis	0	M0: 31 NS: 4	M0: 17; M1: 3; NS: 5	M0: 19 M1: 2	N0: 10 NS: 3	M0: 21 M1: 12 (8 in lung) NS: 6	M0: 20 M1: 4 NS: 1	Stage IVb: 11	M1: 4
Treatment									
Surgical resection	43 (NS 11)	31 (NS 4)	18 (NS 4)	20	8 (NS 3)	29 (NS 4)	19 (NS 2)	0 (NS 5)	24 (NS 2)
Chemotherapy	0	0	18 (NS 6)	0	0	0	8	38 (NS 5)	3 (NS 2)
Radiotherapy	0	0	1	0	1	0	0	35 (NS 8)	0
Other treatment	0	0	0	MIBG therapy: 1	0	Iodine-131: 19	0	Interferon: 25 (NS 10)	Immuno therapy: 2 (NS 2)
Median FU (months)	8.0	18.8	51.0	42.3	56.5	25.0	18.8	48.2	45.0
Status at last visit									
Alive	54	31	23	18	9	31	17	34	19
Dead	0	0	2	0	0	0	6	1	6
NS	0	5	0	3	4	8	2	8	1

Abbreviations: ACC, adrenocortical carcinoma; FRACTURE, French Very Rare Tumors Committee; FU, follow-up; M0, no metastatic involvement; M1, metastatic involvement; N0, no lymph node involvement; N1, lymph node involvement; NET, neuroendocrine tumor; NS, not specified; PPB, pleuropulmonary blastoma; SPPP, solid pseudopapillary neoplasms of the pancreas; UCNT, undifferentiated nasopharyngeal carcinoma.

After a median follow-up of 48 months (5–98), 33 patients were alive in first complete remission, one patient died after PD, and one was alive with disease (unknown: eight cases). Overall survival at 5 years was 96% (unknown: eight cases).

2.2.8 | Cutaneous melanoma (n = 26)

Among the 26 patients with melanoma, six melanomas were classified as spitzoid melanomas. The main tumor sites were head and neck (nine patients) and extremities (nine patients; nonspecified site: three cases). A lymphatic involvement was present in seven patients. Distant metastases were present in four patients (15%) at diagnosis (central nervous system involvement: two cases; distant lymph node: one case; lung: one case). Among them, one died of disease despite chemotherapy and immunotherapy and another with intracranial melanoma died

despite treatment with pembrolizumab. One patient with lung metastasis was still alive with stable disease, after ipilimumab treatment. The patient with the distant lymph node involvement is currently alive in complete remission (CR)-2 after a local relapse. After a median follow-up of 45 months (range: 5–69), 16 patients were alive in first CR, two in second CR, one was alive with stable disease, and two were alive with PD. Four patients died of PD (unknown: one case). Overall survival at 5 years was 69% (unknown: one case).

2.2.9 | Other tumors

Other groups of borderline or malignant tumors were frequently present in the FRACTURE database. The group of salivary gland tumors represented 27 cases, with 14 mucoepidermoid and seven acinar cell carcinomas as the most frequent histologies.

TABLE 3 Cross-match for very rare tumors' registration in the RNCE and the FRACTURE databases between 2012 and 2015 (for the 14 most frequent tumor type)

Histotypes	RNCE	FRACTURE database	Concordant cases	Discordant cases: RNCE only	Discordant cases: FRACTURE database only
Thyroid cancer	263	26	16	247	10
Melanoma	119	16	15	104	1
Neuroendocrine tumor of the appendix	110	29	14	96	15
Adrenocortical carcinoma	39	17	17	22	-
UCNT	38	27	27	11	-
Aggressive vascular tumor	32	9	3	29	6
Rare ovarian cancer	29	5	5	24	-
Salivary glands tumor	28	16	12	16	4
SPPP	25	19	12	13	7
Pulmonary carcinoma	23	9	9	14	-
Giant cell tumor	23	6	5	18	1
Pleuropulmonary blastoma	19	17	17	2	-
Chondrosarcoma	15	1	1	14	-
Pheochromocytoma	9	15	3	6	12
Total	772	212	156	616	56
Total number of cases	828				

Abbreviations: FRACTURE, French Very Rare Tumors Committee; RNCE: National Registry of Childhood Cancers; SPPP: solid pseudopapillary neoplasms of the pancreas; UCNT: undifferentiated nasopharyngeal carcinoma.

The group of rare pulmonary and pleural tumors (excluding PPB and carcinoid tumor) also represented a significant group of tumors (10 cases). Three of these tumors were mucoepidermoid carcinomas, three NUT carcinoma, one adenocarcinoma, one epidermoid carcinoma, one mesothelioma, and one pulmonary chondroid hamartoma.

Concerning aggressive vascular tumors, 14 cases of kaposiform hemangioendotheliomas were collected in the database. Nine cases of giant cell bone tumors were also described.

Finally, ovarian non-germ-cell tumors were present in a group of 13 patients: five cases of mucinous cystadenoma, two ovarian adenocarcinoma, two ovarian carcinoma, and two serous cystadenoma.

2.3 | Cross-match between the French National Registry of Childhood Cancers and the FRACTURE database

Between 2012 and 2015, 877 cases of VRTs were registered in the RNCE, while during the same period, 250 patients were included in the FRACTURE database.

Taking the 14 most frequent tumor types (Table 3), 828 VRTs were registered between 2012 and 2015 in the two databases. Among these, 156 (19%) were in the two databases, 616 (74%) only in the RNCE, and 56 (7%) only in FRACTURE.

According to these results, VRTs represent a total of approximately 200 new cases per year in France. During the 2012–2015 period covered by our study, the RNCE registered approximately 1920 new tumor cases per year (including hematologic malignancies, Langerhans cells histiocytosis, and low-grade brain tumors). Without guarantee of completeness, about 240 borderline tumors are also registered in the RNCE each year, within an annual total of about 2160 tumors. VRTs thus represent about 10% of all new cases of malignant and intermediate tumors registered each year in children and adolescents in France.

Tumor types registered only in the RNCE were mainly thyroid cancers, melanomas, and NETs of the appendix.

All patients included in the FRACTURE database were treated or managed in specialized pediatric oncology units, and reporting was performed by pediatric oncologists. Concerning the site of care (type of hospital and medical unit) for patients with the 14 main VRT groups exclusively registered in the RNCE, only 48% were treated in a specialized pediatric oncology unit (Table 4). The majority was not treated in specialized pediatric oncology units, but in medical non-oncology units or adult oncology units in university hospitals (133 patients: 22%), in surgical units of university hospitals (129 patients: 21%), or in non-university hospital centers (public or private, excluding cancer centers; 61 patients: 10%). The main discrepancies arise mostly in relation to thyroid cancers, melanoma, and NETs of the appendix, which tend not to be directly treated in pediatric oncologic units.

TABLE 4 Site of treatment for patients with a very rare tumor registered in the RNCE (2012–2015)

Histotypes	Categories of hospital centers concerning VRT exclusively registered in RNCE				Total
	1	2	3	4	
Thyroid cancer	104 (42.1%)	77 (31.2%)	56 (22.7%)	10 (4.0%)	247
Cutaneous melanoma	46 (44.2%)	34 (32.8%)	12 (11.5%)	12 (11.5%)	104
NET of the appendix	35 (36.5%)	7 (7.3%)	17 (17.7%)	37 (38.5%)	96
Aggressive vascular tumors	20 (69.0%)	1 (3.4%)	8 (27.6%)	0	29
Rare ovarian cancers	12 (50.0%)	0	11 (45.8%)	1 (4.2%)	24
Adrenocortical carcinoma	16 (72.7%)	4 (18.2%)	2 (9.1%)	0	22
Giant cell tumor	9 (50.0%)	1 (5.6%)	8 (44.4%)	0	18
Salivary glands tumor	10 (62.5%)	0	5 (31.2%)	1 (6.3%)	16
Chondrosarcoma	11 (78.6%)	0	3 (21.4%)	0	14
Pulmonary carcinoma	8 (57.1%)	2 (14.3%)	4 (28.6%)	0	14
SPPP	10 (77.0%)	2 (15.4%)	1 (7.7%)	0	13
UCNT	8 (72.7%)	3 (2.3%)	0	0	11
Pheochromocytoma	2 (33.3%)	2 (33.3%)	2 (33.0%)	0	6
Pleuropulmonary blastoma	2 (100.0%)	0	0	0	2
Total	293 (48.0%)	133 (22.0%)	129 (21.0%)	61 (10.0%)	616

Note: Categories of hospital centers: 1: specialized pediatric oncology unit; 2: medical non-oncology unit or adult oncology unit in university hospital; 3: surgical unit in university hospital; 4: non-university hospital centers (public or private).

Abbreviations: NET, neuroendocrine tumor; RNCE, National Registry of Childhood Cancers; SPPP, solid pseudopapillary neoplasms of the pancreas; UCNT, undifferentiated nasopharyngeal carcinoma; VRT, very rare tumors.

Concerning patients registered in the RNCE and/or in the FRACTURE database (828 patients), 505 patients (60.9%) were treated in a specialized pediatric oncology unit. The other 323 patients (39.1%) were treated in a medical non-oncology unit in a university hospital (133 patients: 16.1%), in a surgical unit in university hospital (129 patients: 15.6%), or in a non-university/non-cancer center hospital (61 patients: 7.4%). Of these 505 patients, only 212 patients (41.9%) were registered in the FRACTURE database.

3 | DISCUSSION

In recent years, a number of countries have set up their own registries for very rare pediatric tumors in order to better understand these diseases.^{20–23} The Italian TREP project (Project on Rare Pediatric

Tumors) was the first of these when it was launched in 2000.²¹ Overall, 297 patients were registered in this database between 2000 and 2005. Our French experience shows a similar distribution of the different tumors with a median age among those patients registered of about 12 years. The German Pediatric Rare Tumor Group (STEP) was founded in 2006.²³ Between 2008 and 2018, 623 patients with VRTs were registered in STEP registry.²² The inclusion criteria and the type of tumors registered are very similar to those of the FRACTURE database.

Registration in the FRACTURE and the RNCE databases is mainly carried out in pediatric oncology departments. Even though both databases register a significant number of cases each year, there is a significant lack of comprehensiveness in the FRACTURE database (53 cases per year) when compared to the RNCE (193 cases per year), with 74% of patients exclusively registered in RNCE, 7% in FRACTURE, and 19% in both databases. There are several possible explanations for

this difference, including the fact that registration in the FRACTURE database is self-reported by a physician with no specific funding for these inclusions, whereas the RNCE provides funding for time spent in the centers. A dedicated team of clinical research associates proactively collect and cross-check data from many sources, such as medical procedure coding systems and pathology laboratories. Finally, registering patients and providing regular follow-up is a time-consuming process for clinicians receiving no financial support for this extra effort. However, and despite all these difficulties, nearly 500 patients were registered in a 7-year period with a large amount of medical data, thus enabling retrospective studies to improve medical knowledge on such rare entities. However, the objectives of these two databases are different. The RNCE is more exhaustive, as it is a systematic publicly funded collection of data, the completeness of which is checked by using the Information System Medicalization Programme.¹⁷ It provides essentially epidemiological data. In contrast, the FRACTURE database provides clinical data available for clinical studies and patient treatment. Several retrospective studies have already been performed with these medical data, improving knowledge of some rare entities.^{11,13,24–26} A number of these retrospective studies were performed with the collaboration of other European VRT groups that registered their own patients and within the framework of EXPeRT group.^{9,27} Finally, all of these studies allowed the EXPeRT group to build and publish care recommendations for the treatment of such rare diseases.^{5,8}

One specific aim of the national registry is to improve knowledge about cancer epidemiology. Our analysis confirms that VRTs represent a total of nearly 200 new cases per year in France, that is, about 10% of all new cases of tumors registered each year in children and adolescents. This constitutes a significant proportion of cases, therefore justifying the existence of specialized working groups and committees to treat and follow-up these patients as best as possible.

To increase the number of inclusions in the FRACTURE database, more complete information should be provided to pediatric oncologists and surgeons should be better informed. Multidisciplinary consultation meetings also serve as a reminder of the existence of the database and raise awareness of the inclusions.²⁸ However, our study confirms that patient registration in the FRACTURE database is mostly performed by pediatric oncologists, probably because this database was initially developed within the framework of the SFCE. It appears more difficult to regularly remind all physicians treating these rare tumors, particularly in units that take care of types of cancer typically seen in adolescents or adults (like thyroid carcinoma or melanoma), especially in non-university hospitals.

This study also highlighted that many pediatric patients treated for VRTs are not directly managed by pediatric hematologists/oncologists. Therefore, patients with pediatric thyroid cancers are generally treated by dedicated endocrinologists, patients with cutaneous melanomas by adult dermatologists, those with NETs by surgeons, and so forth. In these situations, pediatricians may not be involved in the treatment of such patients, which is a matter of concern for several reasons. First, in some cases, the same pathology may require different managements between adults and children; for example,

hemicolecotomies are not indicated in the treatment of NETs of the appendix in childhood,²⁹ or radiotherapy dosages might sometimes be reduced for teenage and young adult patients with UCNT after a favorable tumor response to initial chemotherapy.^{8,14} Second, pathologies can differ in their biology (e.g., childhood melanomas^{25,30}) or etiology (e.g., thyroid carcinoma and *DICER1* syndrome^{31,32}) in pediatric cases and therefore need to be considered specifically in the light of the patient's age. Pediatric oncologists seem to be solicited mostly to manage patients with the most complex cases, as suggested by the proportion of metastatic forms of melanoma, which is three times higher in the FRACTURE database than in the literature (15% vs. 5%).³⁰ Previous studies have shown that children and adolescents with metastatic melanomas are more often managed in pediatric oncology departments than other patients with more localized melanomas.³³

4 | CONCLUSIONS

This study confirmed the great diversity of VRTs in children, which nevertheless represents 10% of all pediatric cancers diagnosed each year. After 10 years of operation, the main goal of the FRACTURE database has been achieved. Enough patients have been registered to enable the database to contribute to all collaborative studies undertaken with other European countries and for researchers to perform collaborative retrospective studies. As a result, several collaborative national and international studies have already been finalized using these data, and have even led to recommendations on the diagnosis and treatment of some VRTs, such as pancreatoblastoma or ACC.^{7–9,27,30,34} The sustainability of this collection is therefore important, and a regular systematic collaboration between the FRACTURE database and the RNCE register helps to provide a more exhaustive picture of these VRTs and allows research completeness for specific groups of patients.

Overall, 39.1% of children and adolescents with these VRTs were not treated in or linked to a specialized pediatric oncology unit. Communication on these rare pathologies and their specificities according to the age of onset must be a major objective of the working groups on VRTs in children and adolescents.

ACKNOWLEDGMENTS

The authors would like to thank Mr Jean-Marie Chrétien, Head of the Data Science Department at CHU Angers, for his involvement in setting up and maintaining the FRACTURE database. The French FRACTURE database is supported by the “Enfant, cancers et santé” association, which did not take part in any of the analyses in this manuscript.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

FUNDING INFORMATIONS

French FRACTURE database supported by “Enfant, cancers et santé”

REFERENCES

1. Desandes E, Faure L, Guissou S, et al. Infant cancers in France: Incidence and survival (2000–2014). *Cancer Epidemiol.* 2020;65:101697. <https://doi.org/10.1016/j.canep.2020.101697>
2. Ferrari A, Brecht IB, Gatta G, et al. 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. *Eur J Cancer* 2019;110:120–126. <https://doi.org/10.1016/j.ejca.2018.12.031>
3. Römer T, Franzen S, Kravets H, et al. Multimodal treatment of nasopharyngeal carcinoma in children, adolescents and young adults - extended follow-up of the NPC-2003-GPOH Study Cohort and patients of the interim cohort. *Cancers.* 2022;14(5):1261. <https://doi.org/10.3390/cancers14051261>
4. Ferrari A, Schneider DT, Bisogno G, et al. Facing the challenges of very rare tumors of pediatric age: the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) background, goals, and achievements. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e28993. <https://doi.org/10.1002/pbc.28993>
5. Orbach D, Ferrari A, Schneider DT, et al. The European Paediatric Rare Tumours Network - European Registry (PARTNER) project for very rare tumors in children. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e29072. <https://doi.org/10.1002/pbc.29072>
6. 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(6):416–420. <https://doi.org/10.1055/s-0032-1327608>
7. Bisogno G, Sarnacki S, Stachowicz-Stencel T, et al. Pleuropulmonary blastoma in children and adolescents: the EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e29045. <https://doi.org/10.1002/pbc.29045>
8. Ben-Ami T, Kontny U, Surun A, et al. Nasopharyngeal carcinoma in children and adolescents: the EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e29018. <https://doi.org/10.1002/pbc.29018>
9. Virgone C, Roganovic J, Vorwerk P, et al. Adrenocortical tumours in children and adolescents: the EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e29025. <https://doi.org/10.1002/pbc.29025>
10. Bien E, Roganovic J, Krawczyk MA, et al. Pancreatoblastoma in children: EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e29112. <https://doi.org/10.1002/pbc.29112>
11. Orbach D, André N, Brecht IB, et al. Mesothelioma in children and adolescents: the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) contribution. *Eur J Cancer.* 2020;140:63–70. <https://doi.org/10.1016/j.ejca.2020.09.011>
12. Stachowicz-Stencel T, Orbach D, Brecht I, et al. Thymoma and thymic carcinoma in children and adolescents: a report from the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT). *Eur J Cancer.* 2015;51(16):2444–2452. <https://doi.org/10.1016/j.ejca.2015.06.121>
13. Picard C, Faure-Contier C, Leblond P, et al. Exploring heterogeneity of adrenal cortical tumors in children: the French pediatric rare tumor group (FRACTURE) experience. *Pediatr Blood Cancer.* 2020;67(2):e28086. <https://doi.org/10.1002/pbc.28086>
14. Jouin A, Helfre S, Bolle S, et al. Adapted strategy to tumor response in childhood nasopharyngeal carcinoma: the French experience. *Strahlenther Onkol.* 2019;195(6):504–516. <https://doi.org/10.1007/s00066-019-01461-6>
15. Dumont B, Fresneau B, Claude L, et al. Pattern of loco-regional relapses and treatment in pediatric esthesioneuroblastoma: the French very rare tumors group (FRACTURE) contribution. *Pediatr Blood Cancer.* 2020;67(4):e28154. <https://doi.org/10.1002/pbc.28154>
16. Vermersch S, Arnaud A, Orbach D, et al. Multicystic and diffuse malignant peritoneal mesothelioma in children. *Pediatr Blood Cancer.* 2020;67(6):e28286. <https://doi.org/10.1002/pbc.28286>
17. Lacour B, Guyot-Goubin A, Guissou S, Bellec S, Désandes E, Clavel J. Incidence of childhood cancer in France: National Children Cancer Registries, 2000–2004. *Eur J Cancer Prev.* 2010;19(3):173–181. <https://doi.org/10.1097/cej.0b013e32833876c0>
18. Poulalhon C, Goujon S, Marquant F, et al. Factors associated with 5- and 10-year survival among a recent cohort of childhood cancer survivors (France, 2000–2015). *Cancer Epidemiol.* 2021;73:101950. <https://doi.org/10.1016/j.canep.2021.101950>
19. Childhood cancer survival in France, 2000–2008. *Eur J Cancer Prev.* 2014, 23(5):449–457.
20. Balmant NV, de Souza Reis R, de Oliveira Santos M, de Camargo B, Gatta G. Rare cancers in childhood and adolescence in Brazil: first report of data from 19 population-based cancer registries. *Cancer.* 2019;125(15):2638–2646. <https://doi.org/10.1002/cncr.32121>
21. 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(4):654–659. <https://doi.org/10.1016/j.ejca.2006.08.028>
22. Hippert F, Desing L, Diez S, et al. Rare tumors in children and adolescents - the STEP Working Group's evolution to a prospective registry. *Klin Padiatr.* 2022;234(3):146–153. <https://doi.org/10.1055/a-1675-3145>
23. Brecht IB, Graf N, von Schweinitz D, Frühwald MC, Bielack SS, Schneider DT. Networking for children and adolescents with very rare tumors: foundation of the GPOH Pediatric Rare Tumor Group. *Klin Padiatr.* 2009;221(3):181–185. <https://doi.org/10.1055/s-0029-1220705>
24. de Tersant M, Généré L, Freyçon C, et al. Pheochromocytoma and paraganglioma in children and adolescents: experience of the French Society of Pediatric Oncology (SFCE). *J Endocr Soc.* 2020;4(5):bvaa039. <https://doi.org/10.1210/jendso/bvaa039>
25. Brecht IB, De Paoli A, Bisogno G, et al. Pediatric patients with cutaneous melanoma: a European study. *Pediatr Blood Cancer.* 2018;65(6):e26974. <https://doi.org/10.1002/pbc.26974>
26. Rod J, Orbach D, Verité C, et al. Surgical management of thymic epithelial tumors in children: lessons from the French Society of Pediatric Oncology and review of the literature. *Pediatr Blood Cancer.* 2014;61(11):1910–1915. <https://doi.org/10.1002/pbc.25159>
27. Surun A, Schneider DT, Ferrari A, et al. Salivary gland carcinoma in children and adolescents: the EXPeRT/PARTNER diagnosis and treatment recommendations. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e29058. <https://doi.org/10.1002/pbc.29058>
28. Benoit C, Orbach D, Cyrille S, et al. Head and neck tumors in children and adolescents: impact of a multidisciplinary tumor board. *Oral Oncol.* 2021;114:105145. <https://doi.org/10.1016/j.oraloncology.2020.105145>
29. de Lambert G, Lardy H, Martelli H, Orbach D, Gauthier F, Guérin F. Surgical management of neuroendocrine tumors of the appendix in children and adolescents: a retrospective French multicenter study of 114 cases. *Pediatr Blood Cancer.* 2016;63(4):598–603. <https://doi.org/10.1002/pbc.25823>
30. Ferrari A, Lopez Almaraz R, Reguerre Y, et al. Cutaneous melanoma in children and adolescents: the EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer.* 2021;68(Suppl 4):e28992. <https://doi.org/10.1002/pbc.28992>
31. Schultz KAP, Williams GM, Kamihara J, et al. DICER1 and associated conditions: identification of at-risk individuals and recommended surveillance strategies. *Clin Cancer Res.* 2018;24(10):2251–2261. <https://doi.org/10.1158/1078-0432.CCR-17-3089>
32. Wasserman JD, Sabbaghian N, Fahiminiya S, et al. DICER1 mutations are frequent in adolescent-onset papillary thyroid carcinoma. *J Clin Endocrinol Metab.* 2018;103(5):2009–2015. <https://doi.org/10.1210/je.2017-02698>

33. Offenmueller S, Leiter U, Bernbeck B, et al. Clinical characteristics and outcome of 60 pediatric patients with malignant melanoma registered with the German Pediatric Rare Tumor Registry (STEP). *Klin Padiatr*. 2017;229(6):322-328. <https://doi.org/10.1055/s-0043-118662>
34. Bien E, Roganovic J, Krawczyk MA, et al. Pancreatoblastoma in children: EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer*. 2021;68(Suppl 4):e29112. <https://doi.org/10.1002/pbc.29112>

How to cite this article: Mallebranche C, Reguerre Y, Fresneau B, et al. The French FRACTURE database: A way to improve knowledge on management of children with very rare tumors. *Pediatr Blood Cancer*. 2022;69:e30003. <https://doi.org/10.1002/pbc.30003>