CHAPTER 4
Specific tumor sites (part 4)

Contents

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Rare tumors

Several diseases fall into the category of rare tumors. They can be summarized as follows:

- tumors in uncommon sites (e.g., eye, bone);
- tumors with uncommon morphology but in a common site;
- tumors of ectopic tissues;
- tumors with atypical morphology for the given site (forms for which ICD-O-3 specifies a site that does not correspond to the recorded site);
- tumors with morphology with atypical behavior (forms with behavior that is not included in ICD-O-3);
- common tumors, incident in uncommon age class (e.g., mesothelioma in youth).

As a general rule, they are cases for which registries must collect all documentation that may prove useful to confirm the diagnosis. Since:

- for tumors in uncommon sites, the loss of even a single case (or the accreditation of a dubious case) generates substantial changes in rates;
- in the other cases, case revision is very likely to be required, whether as a result of using case assessment software (*IARCtools*, *DEPedits*), or as part of an assessment procedure by the AIRTUM Database or the IARC.

However, once all appropriate checks have been run, the best approach is not to rebut the clinical diagnosis, especially if it is supported by solid documentation. Where possible, review and data comparison with special registries (mesothelioma, retinoblastoma, bone, etc.) is recommended for reciprocal enrichment and completion.

Childhood cancer

Tumors arising in childhood (0-14 years) present significant differences compared to those arising in adults:

- they account for 1%-2% of all tumors diagnosed in lifetime;
- Incidence rates are 140-180 cases per million children per year;
- after congenital malformations and accidents, they are the most frequent causes of death in children of ages 1-14;
- their histotype, distribution, and prognosis are different from tumors arising in adulthood: leukemias are the most frequent kind of neoplasm, followed by tumors of the central nervous system and lymphomas; the highest frequency of cases is observed in children between 0 and 4 years of age (42.5%); for most sites and/or histotypes, frequency is higher in males;
- pediatric oncologists are faced with therapeutic choices that strive to balance effectiveness and the risk of relevant negative effects on the future life of their little patients.

The role of childhood population-based registries is therefore specific and can answer different new needs arisen over the past few years in the clinical and organizational field.

However, specific problems concerning casefinding and registration of childhood cancer may arise.

- Diagnosis and hospitalization processes for childhood tumors are different than those for adult tumors.
- Some histotypes (retinoblastoma, neuroblastoma, Wilms's tumor) are only observed in childhood.
- Childhood cancer registries also register benign endocranial tumors.
- Some diseases are borderline and are reported only if they have malignant features (teratomas and reticulo-histiocytosis).
- Histological diagnosis is essential for correct classification (the classification which is currently in use is the *International Childhood Cancer Classification,* ICCC[1]); case review for histology that is not typical for patients' age is included among the checks performed by the *Child-CHECK Program*. Cancer sites are less relevant than in the adult and play a more marginal role in classification.
- For leukemia and non-Hodgkin's lymphomas, it is useful to also have an immunological classification.
- Incidence analysis should be performed by different age classes from the standard five-year age classes; in particular, it is important to measure incidence in the first year of life. This requires both annual populations and dates of birth, of incidence, and follow-up to be at least in month and year format.
- Special registries and general registries give different consideration in their casefinding procedures to the contribution of pathology reports (greater for general registries) and direct hospital record review (greater for childhood registries). This can be a critical problem for leukemia, which in large clinics can have an initial diagnosis made in a clinic laboratory and an in-depth diagnosis made at laboratories that work for the entire network of pediatric oncologists (e.g., the Padua lab). Blood and bone marrow cytology, furthermore, are

often seen by the hematologist in the hospital and not found in the pathology lab report.
- Search for cases hospitalized in another region requires different methods for adults and children.

Travel rates for childhood cancer care are high, but travel is almost entirely towards pediatric oncology centers belonging to the Italian Childhood Hematology and Oncology Association (AIEOP). Brain tumors (patients are admitted to neurosurgery wards) and retinoblastomas (treatment is sought abroad) are an exception. An emerging problem is that of finding cases that were resident abroad and moved to Italy after diagnosis. It is recommended to carry out systematic review of vital statistics at the town of residence prior to reporting the case in the registry, both for living and deceased patients, to check errors that may have been introduced due to the care-related traveling. Furthermore, all personal data and not just life status are thus checked at the closing of the casefinding phase. On the other hand, the gravity of prognosis (cancer is the second cause of death in children over one in Italy) and the age of onset call for studies to identify genetic, environmental, and iatrogenic risk factors and to evaluate population survival data as an index of progress in diagnosis and treatment.

Childhood cancer registries (CCRs) are therefore useful in providing an answer to the questions that have emerged following the development of pediatric oncology over the last decades, through active regional reporting of cases by pediatric oncologists, in part through the AIEOP databases. The limitation, to date, is the presence of CCRs only in few Italian regions; in the other regions, incidence, survival, and trends for childhood cancer are only available thanks to general population-based registries. Therefore, two types of approach are possible.

- Registries operating in areas covered by a CCR should make agreements with it to streamline casefinding and reporting. To this end, active casefinding in pediatric oncology and oncological hematology facilities (e.g., specialized childhood hospitals) that cooperate directly with the CCR can be replaced by passive casefinding through the CCR; this also serves the purpose of saving these facilities a duplicate workload for these activities. Conversely, in general hospitals it is the registries that must perform active casefinding, retrieving all the data needed to provide the partnering CCR with useful data, thus implementing an equal exchange of information.
- Registries operating in areas that are not covered by any CCR, active casefinding and reporting of pediatric cases must be carried out, precisely because of their influence on population rates; standard CCR procedures may be followed (see below). If there are migration trends towards their areas of coverage, registries may establish relations and agreements with interested CCRs.

In general, especially for new registries, it must be ruled out that the case was already incident, perhaps many years before, since patients undergo strict clinical follow-ups and frequently present long survival, at least in the case of hematological cancers. Furthermore, it is not uncommon for patients to often change residence, even as a consequence of their disease. Vital statistics and medical records must therefore be reviewed, and if necessary the caring pediatrician or general practitioner should be contacted, so as not to include prevalent cases or cases not resident at diagnosis in incidence.

Finally, it must be noted that childhood tumors are classified according to the *International Childhood Cancer Classification* (*IARC Technical report* no. 29) with the classification variant proposed by the SEER (**Table 1**, page 6), and that pediatric cases should be checked using the *Child-CHECK* software.

In the following pages, we report the experience of the Piedmont Childhood Cancer Registry (RTIP) in the registration of childhood cancer.

Piedmont childhood cancer registry

The Piedmont Childhood Cancer Registry, founded in 1967, is part of the University service of cancer epidemiology of the San Giovanni Battista hospital in Turin, which is part of the epidemiology and cancer prevention center in Piedmont (CPOPiemonte). It was the first childhood cancer registry in Italy, and it covers one of the largest childhood cancer registry populations in southern Europe. From 1967 to 2003, 3,877 cases were registered of subjects aged 0-14, resident in Piedmont at the time of diagnosis.

The PCCR currently reports incident cases for subjects 0-14 years of age (i.e., from birth to the day prior to the 15th birthday) and is currently carrying out a survey based on HDDs to estimate incidence of cancer in ages 15-19.

Data sources

The goal of completeness and exhaustiveness, common to all registries, requires careful monitoring over time of changes in the diagnosis-treatment process (increase of concourse in Italian and foreign specialist clinics, evolution of the therapeutic approach with greater integration between oncologists, radiotherapists, and surgeons), and identification of new sources of data (automatic registration of hospital discharges, archives of mortality data, lists of cases included in national therapeutic protocols, archives of foreign hospital admissions, to cite only a few). Casefinding therefore is

done by reviewing data from various reporting facilities, both regional and extra-regional. Interactive comparison of sources to confirm and verify acquired data is therefore essential, and it is carried out thanks to the skilled work of secretaries, epidemiologists, statisticians, and pediatricians.
Children with suspected diagnosis of tumor are generally referred from the general practitioner to a hospital pediatrics ward where they undergo the first diagnostic procedures; they are then usually admitted to a specialist ward to complete examinations and undergo therapy. Children transfers usually have emergency status.
As a general rule, the personal and clinical data needed for case inclusion are collected by direct review of the clinical record. At times it is difficult to find documentation for cases that did not follow the normal diagnostic process: in these cases, it can be useful to also contact the family doctor. Both hospital directorates and heads of department are generally asked for permission to review the documentation.
Special attention needs to be paid to certain tumors which require only surgical therapy (e.g., CNS tumors, Wilms's tumor), or which are largely treated abroad (e.g., retinoblastoma), or which arise most frequently in borderline ages and can therefore lead to hospitalization in non-pediatric clinics (osteosarcoma, lymphoma).

Clinical records

Active casefinding is carried out by a registrar who reviews registers, lists, and clinical records of general and specialist pediatrics wards (oncology, neuropsychiatry, endocrinology, orthopedics, etc.) as well as of internal medicine, hematology, neurosurgery, and radiotherapy clinics.
Travel flows for childhood cancer care towards Piedmont and from Piedmont to other regions basically balance out. Almost all hospital admissions are in highly specialized clinics. Children's hospital Regina Margherita is the regional reference center for this type of disease. The most important Italian centers outside Piedmont are included systematically in the casefinding procedures. (Istituto nazionale dei tumori, Istituto neurologico Besta and the Milan and Monza university centers, Istituto G. Gaslini in Genoa, Istituto ortopedico Rizzoli in Bologna, and S. Matteo Hospital in Pavia), chosen on the basis of information on the flow of pediatrics patients from Piedmont. Clinical records of cases identified from archives are also requested (Mod.1.01, hospital admission, hospitalization abroad, HDDs).

Pathology laboratory archives

Casefinding is also carried out at the three regional pathological anatomy service providers (out of about 40) that are relevant for this type of disease. For the past few years, these archives have offered the possibility of carrying out an automatic search by type of diagnosis.

Mortality archives

The regional archive of causes of death, managed by the Piedmont Cancer Registry and which provides a list of deaths from cancer, is also reviewed. For cases found through the mortality archive, clinical documentation confirming diagnosis of cancer is sought out, including through request for information from the patients' physician. Only cases for which this search proves unproductive remain classified as DCO. As of today, DCI cases are not reported.

Other sources

The lists of cases of AIEOP Centers are also reviewed; they are provided directly by the managers of Database Mod.1.01 of AIEOP (professor Pession, Bologna). Further cases reviewed include lists of cases hospitalized abroad, found through archives of authorizations of foreign hospital admissions available from regional health offices or Local Health Units. A copy of the clinical record is requested for all new cases.

Hospital discharge data (HDD)

The regional and extra-regional HDD archive is used as a last resource to find cases that could have been missed. This task is burdensome and yields few results, because most findings correspond to errors in the data registered in the archive. It is, nonetheless, an essential procedure to verify casefinding completeness.
The proportion of new cases found through the HDD archive is below 5% of CCR registered cases. HDDs undergo automatic probabilistic record linkage (EPILINK software) with the Piedmont Childhood Cancer Registry. Records found this way undergo further review before a copy of the clinical record is requested: in particular, records for which the combination of diagnosis, hospitalization duration, and ward makes it unlikely that the case be of interest for the CCR.

Office of vital statistics

Verification of vital statistics for newly registered cases (biennial recording) is performed every other year at the towns of residence and/or birth. Every 4-5 years, follow-up for update of life status is performed for all CCR cases.

Reporting of second neoplasms

Cases of second malignant neoplasm that fall into the CCR reporting criteria (age, diagnosis, residence), are included in the CCR database. An annotation referring to the first tumor case is made in the reporting chart for the second tumor, and vice versa. Second malignant neoplasms falling into this category are currently about

15. CCRs gather information regarding second tumor cases for the entire lifetime of patients. Second neoplasms are reported in the file of the first tumor (and of the clinical documentation request), but they do not constitute additional CCR cases.
Reporting sources are: pediatrics wards, which are often in touch with patients even when they have grown up; HDDs; periodic reviews at GP offices and oncology departments. For this activity, even benign tumors, at any site, are reported.

Definition of cases and type of data collected

The registry records cases with malignant tumors (and cases of benign endocranial tumors) diagnosed from birth to the completion of the 15th year of age, resident in Piedmont at diagnosis.
The date of diagnosis is defined by the histological examination date, or that of the bone marrow aspiration biopsy for leukemia; When histological confirmation is absent, the date of the examination that led to cancer diagnosis or the date of hospital admission are used. Histological or hematological confirmation of diagnosis is available in 90% of cases, with limited variations in the periods considered. Cases exclusively found through death certificate (DCO) were 63 (4% in the period 1967-1969, then progressively dwindling to insignificant numbers in more recent times): for these cases, the date of death was used as the date of diagnosis. Residency is ascertained at municipal registers.
For each registered case, reported information includes vital statistics (date and town of birth, town of residence at diagnosis, town of death, if applicable), the date of diagnosis, the site and type of cancer, the main diagnostic procedures, the name of the hospitals where the child was treated, relevant clinical information at diagnosis (disease extension, white cell count for leukemia, indications on treatment, presence of congenital malformations or any other disease with onset preceding cancer diagnosis, family history of cancer), and the reporting sources (e.g., the hospital discharge archive). Vital statistics of parents and siblings are also registered, along with those of any spouse or child for subjects who are over 18 at the last follow-up.
To enable specific studies to be carried out, the database has been recently enriched by the addition of further clinical information, such as the presence of other tumors after the first diagnosis, data on bone marrow transplant performed on children with leukemia, and genetic data on leukemia and neuroblastomas.
Coding of cancer sites and histological types follows ICD-O (2 and 3) morphology and topography codes. The *Child-Check Program* provided by the IARC makes it possible to automatically transcode ICD-O codes into the ICCC classification system. Furthermore, a special code has been developed for histological diagnosis; the code takes into account some peculiarities of childhood cancers (e.g., bilateralism, immunological subclassification of leukemias).
Data control is carried out with computerized procedures that search for aberrant values and unlikely combinations.
The *Child-Check Program* and locally developed check routines are employed.

Types of study

The Piedmont Childhood Cancer Registry regularly estimates incidence rates, mortality rates, prevalence rates, and survival rates.
Besides publishing these routine statistics, which are particularly useful for public health systems because they make monitoring and planning of assistance policies possible, the RTIP also carries out specific studies on particular aspects related to peculiar characteristics of childhood cancer:

- study on factors correlated with early mortality in the 28 days following cancer diagnosis;
- study on factors correlated with late mortality after 5 years from cancer diagnosis;
- cohort study on mortality among parents of children with cancer;
- estimate of incidence of secondary tumors;
- studies on the quality of life of long-surviving patients;
- methodological studies.

The rarity of childhood cancers and the need to compare experiences and data of the registries of other countries have led CCRs to undertake cooperative studies such as the following:

- ROT, Italian off-therapy registry, which is part of the AIEOP (Italian Childhood Hematology and Cancer Association) it collects clinical information on all treatment received by subjects and on any complications that occurred during treatment of subjects off therapy after a diagnosis of childhood malignancy;
- SETIL, Italian multicentric epidemiology study on the pathogenesis of lymphohematopoietic cancer and neuroblastomas in children;
- ACCIS, Automated Childhood Cancer Information System, IARC Lyons: it collects, presents, and interprets data on the incidence of childhood cancer and the survival of children and adolescents in Europe;
- EUROCARE studies differences between countries and survival trends in children diagnosed with malignant tumors in Europe.

Reference

1. Kramárová E, Stiller CA. The International Classification of Childhood Cancer. Int J Cancer 1996; 68: 759-65.

Table

Table 1. Childhood cancer classification BACK

ICCC codes		Description	ICCC codes modified by SEER
Leukemia	IA	Non acute lymphoid leukemia	011
	IA	Acute lymphoid leukemia	012
	IB	Acute leukemia, excl. acute myeloid leukemia	013
	IC	Chronic myeloid leukemia	015
	ID	Other specified leukemias	016
	IE	Leukemias, NOS	017
Lymphomas and reticuloendothelial neoplasms	IIA	Hodgkin's lymphoma	021
	IIB	Non-Hodgkin's lymphoma	022
	IIC	Burkitt's lymphoma	023
	IID	Miscellaneous lymphoreticular neoplasms	024
	IIE	Lymphomas, NOS	025
CNS and miscellaneous intracranial and intraspinal neoplasms	IIIA	Ependymoma	031
	IIIB	Astrocytoma	032
	IIIC	Primitive neuroectodermal tumors	033
	IIID	Other gliomas	034
	IIIE	Miscellaneous intracranial and intraspinal neoplasms (except germ-cell neoplasms = XA)	035
	IIIF	Unspecified intracranial and intraspinal neoplasms	036
Sympathetic nervous system tumors	IVA	Neuroblastoma and ganglioneuroblastoma	041
	IVB	Other sympathetic nervous system tumors	042
Retinoblastoma	VA	Retinoblastoma	051
Renal tumors	VIA	Wilms's tumor, rhabdoid and clear cell sarcoma	061
	VIB	Renal carcinoma	062
	VIC	Unspecified malignant renal tumors	063
Hepatic tumors	VIIA	Hepatoblastoma	071
	VIIB	Hepatic carcinoma	072
	VIIC	Unspecified malignant hepatic tumors	073
Malignant bone tumors	VIIIA	Osteosarcoma	081
	VIIIB	Chondrosarcoma	082
	VIIIC	Ewing's sarcoma	083
	VIIID	Other specified malignant bone tumors	084
	VIIIE	Unspecified malignant bone tumors	085
Soft-tissue sarcomas	IXA	Rhabdomyosarcoma and embryonal sarcoma	091
	IXB	Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	092
	IXC	Kaposi's sarcoma	093
	IXD	Other specified soft-tissue sarcomas	094
	IXE	Unspecified soft-tissue sarcomas	095
Germ-cell, trophoblastic and other gonadal tumors	XA	Intracranial and intraspinal germ-cell tumors	101
	XB	Other non-gonadal germ-cell tumors	102
	XC	Gonadal germ-cell tumors	103
	XD	Gonadal carcinomas	104
	XE	Other and unspecified malignant gonadal tumors	105
Carcinomas and other malignant epithelial neoplasms	XIA	Adrenocortical carcinoma	111
	XIB	Thyroid carcinoma	112
	XIC	Nasopharyngeal carcinoma	113
	XID	Melanoma	114
	XIE	Skin carcinoma	115
	XIF	Other and unspecified carcinomas	116
Other and unspecified malignant neoplasms	XIIA	Other specified malignant tumors	121
	XIIB	Other unspecified malignant tumors	122
Not classified		Not classified by ICCC	999