Chapter 3. Classification of tumours

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INTERNATIONAL CLASSIFICATION SYSTEMS OF CHILDHOOD NEOPLASMS

The types of cancers that affect children are different from those that occur most commonly in adults. Malignancies of the haematopoietic system are most common; they comprise about 40% of cases before age 20 years and less than 10% of cases after age 20 years [1]. Among all cancers, the proportion of tumours of the CNS before age 20 years is more than 10 times that in the population older than 20 years [1]. A range of tumours arising from embryonal tissues (various blastomas) occur almost exclusively in young children, and neuroblastoma is the most common cancer in the first year of life in high-income countries.

In general, most cancers occur among mature adults [2], and most of them develop in epithelial tissues as carcinomas [1]. The common sites that constitute the major cancer burden in the total population are carcinomas of the breast, prostate, lung, colorectum, cervix uteri, and stomach. It is usual to present the overall cancer burden in a population according to the primary site of the tumour, in agreement with the major categories defined in the successive revisions of the International Classification of Diseases (ICD) [3]. Presenting childhood cancer data for the same categories holds little interest, because very few cases would be reported for these sites that are common in adults, whereas a large proportion of childhood cancers would not be reported with enough detail.

The spectrum of cancers changes rapidly during the first few years of life [4]; therefore, the overall cancer incidence in each year of age reflects the representation of individual tumour types. The young age of patients and the different histological appearance of tumours may also suggest different etiology of these tumours, which highlights the need for a specialized classification.

In the mid-1970s, a need to describe tumours more specifically than in the ICD series resulted in the publication of the International Classification of Diseases for Oncology (ICD-O) [5]. In ICD-O, the neoplasms chapter of ICD was expanded into more detailed information on the primary site and very detailed information on the morphology (histology, behaviour, and grade). For cancers in children, this information needed to be grouped into meaningful categories describing the disease burden characteristic of the childhood population.

Efforts to appropriately classify childhood cancers appeared as far back as the late 1950s [6–8]. The first internationally adopted classification, proposed by Birch and Marsden in 1987 [9], grouped the tumours coded according to ICD-O [5]. It was used with some modifications [10] in IICC-1 [11] and was revised as the International Classification of Childhood Cancer (ICCC-2) [12] using the ICD-O-2 coding system [13] in IICC-2 [14]. After the publication of the third edition of ICD-O (ICD-O-3) [15], a third edition of the International Classification of Childhood Cancer (ICCC-3) was published in 2005 [16] and used internationally. The first revision of ICD-O-3 (ICD-O-3.1) [17] and the requirement to present international childhood cancer data in IICC-3 stimulated a review of ICCC-3.

Simultaneously, IARC coordinated revisions of the WHO Classification of Tumours [18–32]. In these successive editions, advances in pathological methods and molecular typing of tumours resulted in more up-to-date terminology, the introduction of new entities and ICD-O histology codes, and the removal of obsolete ones. Some of these changes are reflected in ICD-O-3.1 [17].

INTERNATIONAL CLASSIFICATION OF CHILDHOOD CANCER, 3RD EDITION, 2017 UPDATE (ICCC-3-2017)

Based on ICCC-3, which was published in 2005 [16], ICCC-3-2017 was developed to group cancers in IICC-3. This 2017 update incorporates ICD-O-3.1 [17], as well as the new morphology codes proposed in the several publications of the WHO Classification of Tumours series [25–32], although the newly proposed codes may not have been fully integrated in cancer registries by 2017. The principles of ICCC-3-2017 can be summarized as follows.

1. The original coding system with three-level hierarchical organization of the classification categories was retained as far as possible to enable comparisons with previously published data.
2. Newly proposed morphology codes, listed in Table A.4, were incorporated, to anticipate their classification.
3. Classification of all morphology types was reviewed, to align ICCC-3-2017 with the internationally recognized diagnostic and classification advances mentioned above.

The ICCC-3-2017 classification system is shown in Table A.2 and Table A.3. The specific major modifications adopted, compared with ICCC-3, are summarized briefly below and include the following.

1. In addition to maintaining all morphology codes defined in ICD-O-3 [15], the new morphology codes proposed in ICD-O-3.1 [17] and in the WHO Classification of Tumours volumes published in 2010–2017 [25–32] were included. The new morphology codes classified by ICCC-3-2017 are tabulated in Table A.4 if their numerical values were not used in ICCC-3 in 2005 [16].

2. All identified histology codes were classified within ICCC-3-2017, irrespective of the behaviour associated with these codes in the reference publications, in accordance with the matrix rule F of ICD-O [17]. However, outside the CNS, the tumours are classifiable by ICCC-3-2017 only if reported with malignant behaviour.
3. In accordance with the progressive removal of the distinction between leukaemias and lymphomas, in favour of distinguishing the neoplasms by cell of origin [24], the previously unrestricted subgroups Ia and IIb are now restricted for topography, to enable the relevant morphologies to be classified as either leukaemia or lymphoma, depending on their presentation and characterization by a pathologist. Therefore, the relevant morphology types in combination with sites of blood (C42.0), bone marrow (C42.1), reticuloendothelial system (C42.3), and haematopoietic system (C42.4) are classified as lymphoid leukaemias (Ia), whereas in combination with all other sites they are classified as non-Hodgkin lymphoma (except Burkitt lymphoma) (IIb). Both categories comprise precursor lymphoid neoplasms, mature B-cell neoplasms, and mature T- and NK-cell neoplasms as grouped by Swerdlow et al. in 2008 [24].
4. Peripheral neuroectodermal tumour (M-9364) of kidney was transferred from the subgroup of nephroblastoma and other non-epithelial renal tumours (VIa) to the subgroup of other specified soft tissue sarcomas (IXd), so that this histological type is classified in a single tumour group irrespective of the site of occurrence; including skin sites [33] and CNS sites [34].
5. The subgroup of hepatoblastoma (VIIa) was expanded to include mesenchymal tumours of liver (malignant rhabdoid tumour (M-8963) and embryonal sarcoma (M-8991)), which are of considerable clinical and epidemiological interest. The subgroup is renamed as “hepatoblastoma and mesenchymal tumours of liver” and is split into three divisions, separating hepatoblastoma (VIIa1), rhabdoid hepatic tumour (VIIa2), and embryonal sarcoma of liver (VIIa3). M-8991 and M-8963 are now classified in the subgroups rhabdomyosarcomas (IXa) and other specified soft tissue sarcomas (IXd), respectively, only if they occur in sites other than liver and kidney.
6. The changes described in points 4 and 5 resulted in a reduction of the number of divisions from four to three in subgroup VIa, whereby the fourth division defined in ICCC-3 (VIa4, peripheral neuroectodermal tumour of kidney) was abolished in ICCC-3-2017. Simultaneously, three new divisions of the previously undivided subgroup VIIa (point 5) were created; thus, there are two more divisions in ICCC-3-2017 than in ICCC-3.
7. The subgroups of carcinomas (renal (VIb), hepatic (VIIb), gonadal (Xd), adrenocortical (XIa), thyroid (XIb), nasopharyngeal (XIc), skin (XIe), and other and unspecified (XIf)) were modified by including newly defined codes and removing codes inconsistent with the given topography. Some of these changes are specifically mentioned below if they merit a justification; the others are unlikely to have an important impact on the resulting incidence rates.
8. Hepatoid (adeno)carcinoma (M-8576) was removed from kidney carcinomas (VIb), because it was not found as arising from kidney. It is included in the subgroups of gonadal carcinomas (Xd) [35] and other carcinomas (XIf), because it has been described in several sites of the digestive tract (e.g. [36]), lung [37], adrenal gland [38], and endometrium [39], among others.
9. Myxoid chondrosarcoma (M-9231) could be used to describe chondrosarcomas of bone or extraskeletal chondrosarcoma. Therefore, this morphology was added to the subgroup of chondrosarcoma (VIIIb) if occurring in bone and to the subgroup of other specified soft tissue sarcomas (IXd) if occurring in other sites.
10. Melanotic neuroectodermal tumour (M-9363 if malignant) may arise in various sites, including nasal cavity, neurocranial dura of brain, skin, uterus, mediastinum and paratesticular structures; therefore, it is now placed in the subgroup of other specified tumours (XIIa) for all sites.
11. Malignant forms of trophoblastic teratoma (M-9102), partial hydatidiform mole (M-9103), placental site trophoblastic tumour (M-9104), and trophoblastic epithelioid tumour (M-9105) were added to the subgroup of malignant gonadal germ cell tumours (Xc). Simultaneously, M-9102 was removed from the subgroup Xb of extracranial and extragonadal germ cell neoplasms.
12. Several changes in the subgroup of gonadal carcinomas comprised the addition of newly defined codes, the restriction of some codes to ovary or gonads, and the inclusion of the morphologies known to occur only in gonads without a topography restriction.
13. Skin sites of genital organs (C51.9, C60.9, and C63.2) were allowed in the subgroup of skin carcinomas (XIe).
14. Pleomorphic carcinoma (M-8940/3) is placed in the subgroup of other specified tumours (XIIa) irrespective of the primary site.
15. Myoepithelial carcinoma (M-8982/3) is now regarded as a mixed tumour [40]; therefore, it was placed in the subgroup of other specified tumours (XIIa) without a restriction on the primary site.

ALLOCATING NEOPLASMS TO ICCC-3-2017 CATEGORIES

The classification framework outlined in Table A.2 and Table A.3 conveys the classification rules for cancers that were correctly coded. The following summary rules apply to this classification.

1. ICCC-3-2017 can only be used for morphology coded according to ICD-O-3, ICD-O-3.1, or, if needed, the morphology codes listed in Table A.4.
2. Only the codes listed in ICD-O-3 and ICD-O-3.1 and those shown in Table A.4 are classifiable. For example, a code M-8483, which would fall within the range 8480–8586 in XIf, is not classifiable, because it is not recognized in any of these lists.
3. In Table A.2 and Table A.3, the ranges of codes were used for convenience. There may be some histology codes within a range that would not occur in the primary sites listed and some primary site codes within a range that would not have the listed histology

codes. Similarly, the individual morphology codes may not necessarily occur in all listed sites, especially in the diagnostic categories that include many morphology or site codes, such as the subgroup of other and unspecified carcinomas (XIf).

4. Only malignant primary tumours are classifiable within ICCC-3-2017 for all categories except the CNS tumours (main group III and subgroup Xa in Table A.2 and Table A.3), which are classifiable also with non-malignant behaviour.
5. A combination of histology with behaviour not listed in ICD-O-3, ICD-O-3.1, or any of the WHO Classification of Tumours publications referenced in Table A.4 should be classified only if the coding accuracy was double-checked in medical records and confirmed by a pathology report.
6. Despite the great flexibility of the ICD-O system, unlikely combinations of two or more variables, including site, morphology, behaviour, basis of diagnosis, age, sex, and grade, should be double-checked and confirmed by comparison with medical records.
7. To analyse the incidence of primary neoplasms, cases registered with behaviour /6 or /9 should first be recoded to behaviour /3, with appropriate changes to the site and morphology codes, and then classified, using information on the primary tumour of the diagnosis.

IMPACT OF CHANGES IN CLASSIFICATION ON DATA COMPARABILITY

The data in this publication span the period of use of ICD-O-2, ICD-O-3, and ICD-O-3.1, so that registries had to deal with new terminology not included in ICD-O-3 and a choice of histology codes for the case. Different registries have implemented the different ICD-O revisions in different years (Table A.10). These changes will be reflected in the cancer data to a varying extent in different settings and need to be considered when interpreting time trends and geographical variations.

The most pertinent to the target age range of IICC-3 is the change in the coding of behaviour for pilocytic astrocytoma (ICD-O-3 M-9421), which may represent about 20% of CNS tumours before age 15 years [41]. The coding of behaviour for this neoplasm changed from malignant in ICD-O-2 [13] to uncertain in ICD-O-3 [15], and this change may have affected the completeness of registration of this tumour, especially in the registries that exclude non-malignant tumours. The differences in coding of behaviour for pilocytic astrocytoma are combined with differences in coding practices for optic nerve glioma (M-9380, C72.3), which is almost always a pilocytic astrocytoma with behaviour /1 in ICD-O-3.1, although a proportion of them may be coded to a glioma, implying malignant behaviour. It should be borne in mind that a behaviour code for pilocytic astrocytoma probably reflects more the coding practices than the actual way the tumour acts within the body.

In contrast, myelodysplastic syndromes (MDS, M-998) were coded to non-malignant (uncertain) behaviour in ICD-O-2 [13] and to malignant behaviour in ICD-O-3 [15]. This change in the coding practice would have affected the completeness of registration of these neoplasms during the study period.

New histology codes may have extended the previously defined range of histology codes; for example in IXb, the range 8813–8815 in ICCC-3 became 8813–8817 in ICCC-3-2017. A new code may also have been defined within an existing range, in which case no change would show between the classification tables of ICCC-3 and ICCC-3-2017. Sometimes, an ICD-O-3 morphology code changed its meaning in the new edition of the WHO Classification of Tumours series, as in the following example. In ICD-O-3, 9975/1 coded “myeloproliferative disease, NOS” and 9960/3 coded “chronic myeloproliferative disease, NOS”. In ICD-O-3.1, codes 9975/1 and 9960/3 were harmonized into 9960/3 under the header term “myeloproliferative neoplasm, NOS” and included both “myeloproliferative disease, NOS” and “chronic myeloproliferative disease, NOS” as synonyms. In addition, in ICD-O-3.1 a new entity – 9975/3 – was added, to code “myeloproliferative neoplasm, unclassifiable”. This entity is reserved for a clinical diagnosis where there has been a definite diagnosis of myeloproliferative neoplasm but it fails to meet the specific criteria of any of the other myeloproliferative neoplasms. These changes may imply a modification of eligibility for registration, because the new entities mentioned are all malignant, whereas “myeloproliferative disease, NOS” was previously listed with uncertain behaviour.

Often a change concerned only the behaviour code, which was either added to the listed codes or changed. For example, instead of the uncertain behaviour associated with “Langerhans cell histiocytosis, NOS” (9751/1) in ICD-O-3, the same morphology and term is listed only with malignant behaviour (9751/3) in ICD-O-3.1, and the other morphology codes for unifocal (9752/1), multifocal (9753/1), and disseminated (9754/3) Langerhans cell histiocytosis were removed [17]. Changes in the behaviour code may have an impact on reportability, especially in the registries that exclude non-malignant tumours from registration. For example, serous (8442) or mucinous (8472) neoplasms of the ovary with borderline malignancy were registered and coded as malignant (/3) in ICD-O-2, but the associated behaviour code changed to uncertain (/1) in ICD-O-3, and thus their registration may have stopped in some registries. Because both histology codes were linked with a single behaviour code in both editions of ICD-O, a conversion from ICD-O-2 to ICD-O-3 would eliminate these cases to conform to ICD-O-3.

Progress in the recognition and characterization of new morphological entities leads to changes in classification, which may also affect reportability, especially in the registries with restricted eligibility criteria. Examples that could markedly influence variations in incidence rates between registries and over time include pilocytic astrocytoma, myelodysplastic syndromes, skin carcinoma, and carcinoid of appendix, as discussed in the “Eligibility for reporting” section of Chapter 4.

The full impacts of these and other changes in the classification of tumours on incidence rates are difficult to evaluate in individual registries, and even more so on an international level. Specific studies will need to be undertaken to correctly interpret detailed spatial and temporal variation in incidence trends.

FUTURE UPDATES

ICCC-3-2017 was developed to classify all cases submitted to IICC-3 using the latest then-available knowledge in classification of tumours. In this respect, the proposed classification was anticipating the needs, because many of the changes proposed in ICD-O-3.1 or in the WHO Classification of Tumours series may not have been taken up by the pathologists characterizing the tumours for the registries in the data presented in this book and beyond. However, since the 2017 update of ICCC-3, additional changes to histological classification have been proposed, for endocrine tumours [42] and haematopoietic malignancies [43] and several others (https://whobluebooks.iarc.who.int). A second revision to ICD-O-3 (ICD-O-3.2) was released in 2019 and recommended for use as from 2020 [44]. The ICD system was also revised, and ICD-11 was released in 2019 and officially came into effect in 2022 [45]. In addition, a double volume dedicated to paediatric neoplasms has been published for the first time in the WHO Classification of Tumours series [46]. ICD-O-4 was in preparation in 2025 [44].

Although it will take time for these new standards to be implemented by cancer registries, a new update of ICCC-3-2017 is planned to reflect the above-mentioned and forthcoming changes, and the IICC-3 website may serve as an appropriate platform for dissemination.

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