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Towards optimal clinical and epidemiological registration of haematological malignancies: Guidelines for recording progressions, transformations and multiple diagnoses

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Abstract Haematological malignancies (HM) represent over 6% of the total cancer incidence in Europe and affect all ages, ranging between 45% of all cancers in children and 7% in the elderly. Thirty per cent of childhood cancer deaths are due to HM, 8% in the elderly. Their registration presents specific challenges, mainly because HM may transform or progress in the course of the disease into other types of HM. In the context of cancer registration decisions have to be made about classifying subsequent notifications on the same patient as the same tumour (progression), a transformation or a new tumour registration. Allocation of incidence date and method of diagnosis must also be standardised.

We developed European Network of Cancer Registries (ENCR) recommendations providing specific advice for cancer registries to use haematology and molecular laboratories as data sources, conserve the original date of incidence in case of change of diagnosis, make provision for recording both the original as well as transformed tumour and to apply precise rules for recording and counting multiple diagnoses. A reference table advising on codes which reflect a potential transformation or a new tumour is included.

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This work will help to improve comparability of data produced by population-based cancer registries, which are indispensable for aetiological research, health care planning and clinical research, an increasing important area with the application of targeted therapies.

1. Introduction

Haematological malignancies (HM) represent over 6% of all cancers occurring in the European population. It is estimated that more than 232,000 new cases of HM occurred in forty European countries in 2012 and over 120,000 persons died of these conditions. HM affect all age groups, to a different extent (Fig. 1). The five-year prevalence estimate exceeds 575,000 patients [1]. Timely and correct diagnosis is indispensable for efficient disease control.

Difficulties arise for cancer registries in the registration of multiple tumours, in particular, haematological malignancies (HM) which may transform or progress in the course of the disease. HM are thought to arise by genetic change (malignant transformation) of a single cell originally present in bone marrow, thymus or the lymphoid system. The transformed cell undergoes clonal replication and expansion. In many cases further genetic changes take place and the subsequent clones become more aggressive, or transform into a different tumour type [2]. Examples of transformation include myelodysplastic syndrome to acute myeloid leukaemia. HM may be diagnosed at any stage in the process of malignant transformation.

Better understanding of the natural history of these diseases, together with rapid advances in methods for diagnosis and prognosis prediction, has led to improvement in HM classification. These have been reflected in updates to the International Classification of Diseases for Oncology [3–5]. The Haemacare manual [6] provides useful clinical information on HM and their coding and helps explain decision making processes. While excellent for clinicians, it lacks the specific practical advice required by population based or clinical registries for registration of evolution or transformation of HM.

This work which should be considered supplementary to the Haemacare manual and takes account of new morphological codes [5] was undertaken by a Working Group (WG) of Work Package 3 of Eurocourse (www.eurocourse.org) following terms of reference prepared by the Steering Committee of the European Network of Cancer Registries (ENCR) to:

a) Define how cancer registries should record HM undergoing transformation from a tumour with uncertain behaviour (coded /1) to malignant tumour (behaviour coded /3), or from one malignant histology to another and
b) Provide rules for recording and counting multiple diagnoses of HM in the registry database

2. Methods

For this work the WG firstly reviewed the available information on the subject. This included existing ENCR rules [7], the Haemacare manual [6], rules for coding multiple HM from European registries represented in the WG (United Kingdom (UK), Spain, France, Italy and The Netherlands), as well as the Hematopoietic and Lymphoid Database from the Surveillance, Epidemiology, and End Results (SEER) Program from the United States [8]. Based on the existing information new recommendations were made, as well as a list with morphology combinations to support the decision whether to code one or two HM. The latter list was based on an (unpublished) list from the Netherlands and adapted using the expert's opinion of the WG members.

3. Recommendations

3.1. Multiple data sources should be used to register HM

Except for lymphomas, most of the myelodysplastic disorders, myeloproliferative neoplasms and leukaemias may not have a solid tissue diagnosis and definitive diagnosis will be made on haematological preparations alone. Therefore, in addition to histopathology, cytology, clinical records and death notifications, registration of HM requires data on blood, bone marrow, flow cytometry, molecular and cytogenetic tests from haematology and designated molecular laboratories. These specific data sources are required to ensure complete case ascertainment and accurate morphological classification.

As already mentioned in the Haemacare manual [6], cytogenetic analysis is essential for establishing the diagnosis of subgroups of acute myeloid leukaemia (AML), myelodysplastic syndromes (MDS) and chronic myeloid leukaemia (CML), and for identifying other myeloproliferative and lymphoproliferative disorders e.g. through the JAK-2 mutation to confirm polycythaemia vera, t(11;14) translocation to confirm mantle cell lymphoma or the t(8;14) translocation to confirm Burkitt lymphoma. Further detail and examples of these are available in the Haemacare manual [6].

3.2. Registration of multiple notifications

After a newly diagnosed haematological malignancy has been registered, additional information obtained

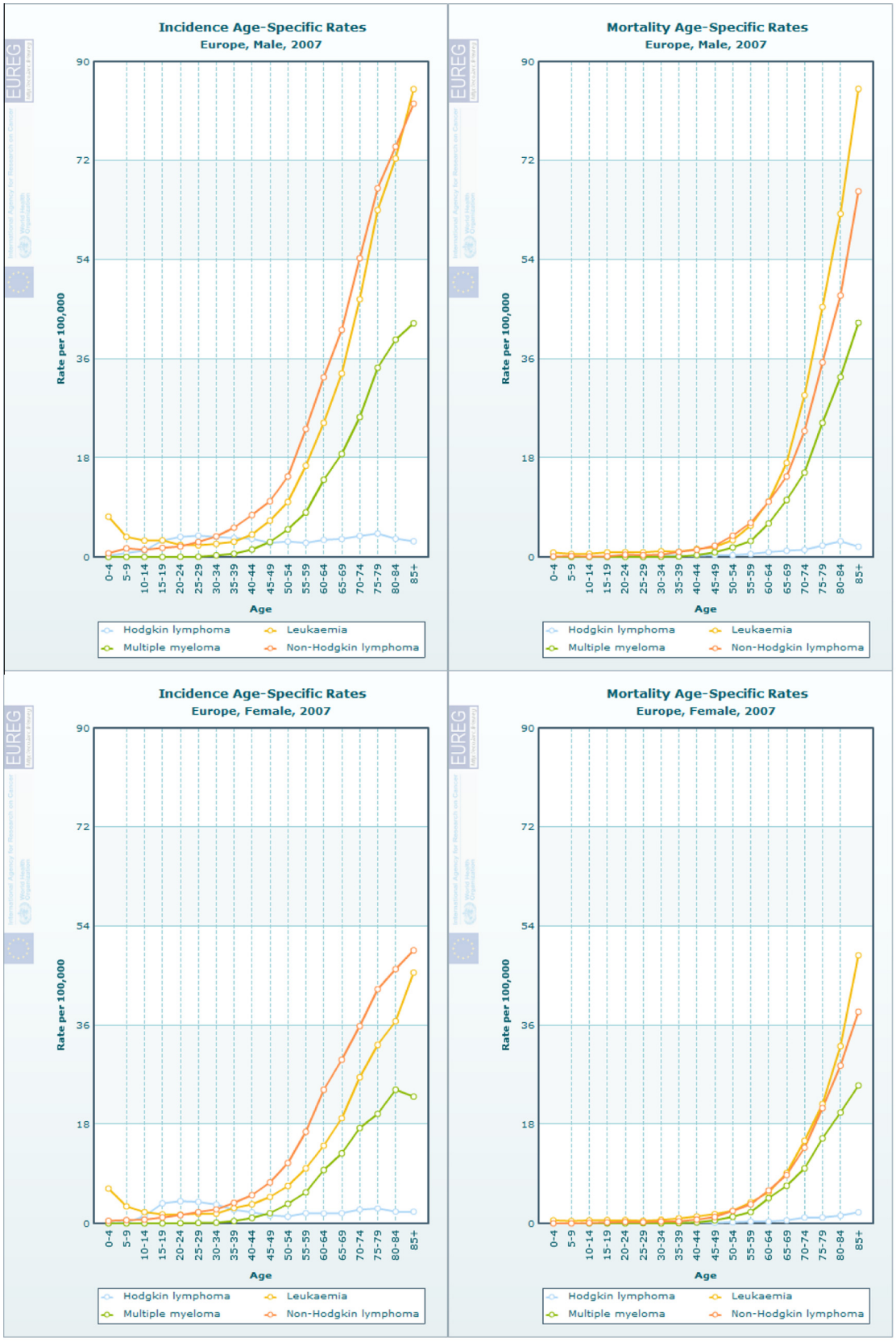

Fig. 1. Haematological malignancies in Europe in 2007: age-specific incidence and mortality rates based on 73 population-based cancer registries providing data to the EUREG database.

by cancer registries for the same patient provides several options for registration.

a. Same tumour, but with a more specific or revised diagnosis
b. Transformation
c. New tumour registration

Table 1 shows for the myelodysplastic syndromes (MDS) potential combinations of morphology codes that can be considered as the same tumour or a transformation. Unspecific codes are underlined. A more extensive table containing all haematological malignancies is available in the appendix. In general, different diagnoses within a diagnostic group of the World Health Organisation (WHO) Classification (such as MDS) will relate to the same tumour. In all cases, the most specific diagnosis should be registered with clinical opinion having the final call. Combinations which are not in the table can be considered as two separate tumours.

3.2.1. Same tumour but with a more specific or revised diagnosis

In HM it is not uncommon that different diagnostic specimens result in a different diagnosis. In general, such different diagnoses within a diagnostic group of the WHO Classification will relate to the same tumour [4]. The most specific morphology code should be registered.

For example, if a patient's medical file has a 'myelodysplastic syndrome' (morphology code 9989), and the laboratory report gives the specific diagnosis of 'refractory anaemia with excess blasts' (morphology code 9983), the latter morphology code should be registered, as according to Table 1 9989/3 and 9983/3 probably refer to the same tumour and 9983/3 is the most specific code (not underlined).

When a pathological specimen/slide is reviewed by an expert pathologist/haematologist/cytologist the expert opinion is considered the definitive diagnosis, but the revision of the diagnosis will not change the already assigned date of incidence. For example, if the initial diagnosis is 'refractory anaemia' (morphology code 9980), while after revision the diagnosis is modified into 'myelodysplastic syndrome with isolated del(5q)' (morphology code 9986), the latter morphology code should be registered.

3.2.2. Transformation

When a HM transforms into a new morphological entity, only the first tumour is to be considered as incident: the transformed tumour must **not** be counted as a new tumour and therefore not be included in the incidence statistics.

If the transformation occurs within three months after the incidence date initially chosen, the morphology code of the transformed malignancy should replace that of the first tumour and be recorded as the first primary and not a transformation. If the transformation occurs outside the three month window, then the morphology code should be recorded as that of the initial malignancy and the morphology of the transformed malignancy, while noted in the registry, must not be included in incidence estimates.

Preferably, registries should record information on original as well as transformed tumours. The transformation/multiple primary rules should then be applied only at the time of analysis. The record of the transformed malignancy should, if possible, also be flagged as transformation. In accordance with the Haemacare

Table 1
Combinations of morphology codes of haematological malignancies (HM) referring to the same tumour or to a potential transformation (only combinations with myelodysplastic syndrome are shown; see the appendix for other combinations).

Initial diagnosis	Morphology code of the first HM	Morphology codes probably referring to the same tumour as the first HM)	Morphology codes referring to potential transformation of the first HM (see note 3)
Refractory anaemia	9980/3	Other myelodysplastic syndromes (MDS)*, 9945/3, 9975/3	Acute myeloid leukaemia (AML)**, 9801/3, 9860/3
Refractory anaemia with ring sideroblasts	9982/3	Other MDS*, 9945/3, 9975/3	AML**, 9801/3, 9860/3
Refractory anaemia with excess blasts	9983/3	Other MDS*, 9945/3, 9975/3	AML**, 9801/3, 9860/3
Refractory cytopenia with multi-lineage dysplasia; Refractory cytopenia of childhood	9985/3	Other MDS*, 9945/3, 9975/3	AML**, 9801/3, 9860/3
Myelodysplastic syndrome associated with isolated del(5q)	9986/3	Other MDS*, 9945/3, 9975/3	AML**, 9801/3, 9860/3
Myelodysplastic syndrome, therapy related	9987/3	Other MDS*, 9945/3, 9975/3	AML**, 9801/3, 9860/3
Myelodysplastic syndrome, NOS	9989/3	Other MDS*, MD/MPN***	AML**, 9801/3, 9860/3
Refractory neutropenia	**9991/3**	Other MDS*, 9945/3, 9975/3	AML**, 9801/3, 9860/3
Refractory thrombocytopenia	**9992/3**	Other MDS*, 9945/3, 9975/3	AML**, 9801/3, 9860/3

Non-specific morphology codes are underlined, morphology codes first introduced in the ICD-O-3 update of 2011 are in bold.
* MDS includes the following morphology codes: 9980/3, 9982/3, 9983/3, 9985/3, 9986/3, 9987/3, 9989/3, 9991/3, 9992/3.
** AML includes the following morphology codes: 9840/3, 9861/3, 9866/3–9874/3, 9891/3, 9895/3–9931/3.
*** MD/MPN (myelodysplastic/myeloproliferative neoplasm) includes the following morphology codes: 9876/3, 9945/3, 9946/3, 9975/3.

manual [6], the following additional items are recommended to be included in the cancer registry database to accommodate the recording of transformations:

- Transformation yes/no
- Date of transformation dd/mm/yyyy
- Topography of transformed HM ICD-O
- Morphology of transformed HM ICD-O

For example, if six months after the diagnosis of a refractory anaemia with excess blasts an acute myeloid leukaemia is diagnosed, this should be considered as a transformation, if within three month period then it would be considered as a first registration of acute myeloid leukaemia with no transformation and date of diagnosis that of the diagnosis of the refractory anaemia. (see Table 1).

3.2.3. A new tumour registration

This occurs when

i. a HM with malignant behaviour (code /3) occurs after a previous haematological disease with uncertain behaviour (code /1) (the later diagnosed malignant HM should be registered as a new tumour with a new incidence date)

or

ii. the change is not a transformation or a revised diagnosis of an existing tumour

or

iii. a clinical opinion regarding a new tumour is available and the details of that decision is recorded.

For example, irrespectively of the time interval between the two diagnoses, two separate tumours should be registered in the case of Hodgkin lymphoma following a myelodysplastic syndrome, (the combination is not in Table 1).

3.3. Survival analysis of multiple tumours/transformations

Regular survival analysis methods do not necessarily apply in the case of patients with HM where transformations have occurred as the patient has to be alive until the diagnosis of multiple tumour or transformation occurs. The information of these changes may be used as time-dependent covariates. There are special methods for such multiple tumour analyses [10].

3.4. The basis of diagnosis follows the ENCR recommendations [7]

In general, code 5 (cytological examination of peripheral blood, bone marrow aspirate or other aspirates) and code 7 (histology of lymph node or tissue biopsy including trephine bone marrow biopsy) are most appropriate for HM. Blood tests e.g. smears should be considered to have the same standing as 'cytology' (code 5).

- Code 1 (physical examination, diagnosis made before death, but without the support of diagnostic modalities) and Code 6 (Histology of metastasis) are not applicable to haematological malignancies.
- Code 4 (specific tumour marker) is applicable for multiple myeloma diagnosed with other criteria using data on serum immunoglobulins or light chain urinary excretion.
- Code 2 (instrumental/surgical examination) may be applicable exclusively for brain lymphoma

3.5. Incidence date

The ENCR recommendations for coding of incidence date should be followed for assigning the incidence date for HM for the purposes of cancer registration [9].

When a pathological specimen/slide is reviewed by a second expert pathologist, the expert opinion is considered the definitive diagnosis, but the original date of incidence does not change.

4. Discussion

This paper provides the guidelines necessary for correct recording of HM, so that the resulting population-based data may monitor the incidence and outcome with as much precision as possible. These data inform the priorities for clinical research as well as health policy decisions.

There are over 600 population-based cancer registries internationally, 300 included in Cancer Incidence in V Continents [11,12], all recording data according to agreed rules on malignant and premalignant diseases for defined populations. Some of them specialise in registration of HM only, either in childhood or in all ages. They monitor disease levels and changes over time, facilitate scientific study of disease causes and patterns, including alleged clusters and enable monitoring of patient care and outcomes including survival. These cancer registries have developed worldwide collaboration and regional networks. Standardised data recording, processing and reporting are indispensable for comparative studies across populations and over time. Presented recommendations are in line with the current classification standards, including pathological classification of HM covered in the WHO, Classification of Tumours of the Haematopoietic and Lymphoid tissue [4], the ICD-O-3 [3] and its update of 2011 [5]. The Haemacare manual provides useful clinical information on HM and their coding and helps explain decision making processes [6]. The current work will supplement the publications mentioned above with specific practical advice for the population-based cancer registries as well as all primary data

providers and may be useful also for clinical cancer registries. It highlights the need for standardised rules for registration, coding and selecting of HMs for analyses.

Incidence statistics serves a basis for aetiological studies, therefore only the first incident tumour will be most of interest. However, to allow for changes in multiple primary rules over time and various research interests, it is important that the registries retain all available data on transformed tumours or successive diagnoses in their databases. Counting only one tumour will also help to keep coherence with the mortality statistics.

Inclusion of cases in the analysis of survival will depend on the question asked. To produce population-based estimates of survival, the first tumour will most often be of interest. However, data should also allow for analysing survival of patients with specific succession of neoplasms or transformations, using the appropriate statistical methods.

The ENCR recommendations for recording of HM were developed by a dedicated working group during 2012 (full report at www.encr.eu) and endorsed by the Steering Committee of ENCR in April 2013. They complement the series of ENCR recommendations on registration practices released between 1995 and 2002 [7]. Their implementation will improve the comparability of incidence and survival data for HM across cancer registries and over time.

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Conflict of interest statement

None declared.

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Appendix

Combinations of morphology codes of haematological malignancies (HM) referring to the same tumour or to a potential transformation.

Major subgroups according to the World Health Organisation (WHO) Classification	Initial diagnosis	Morphology code of the first HM	Major WHO subgroups and morphology codes probably referring to the same tumour as the first HM (see note 3)	Major WHO subgroups and morphology codes referring to potential transformation of the first HM (see note 3)
Myeloproliferative neoplasms (MPN)	Mast cell sarcoma	9740/3	Other MPN (excl. 9742/3)	9742/3, 9741/3
	Systemic mastocytosis	9741/3	See note 1	9742/3, 9741/3, AML (particularly if SM-AHNMD)
	Mast cell leukaemia	9742/3	Other MPN, 9800/3, 9860/3 (see also note 1)	
	Chronic myeloid leukaemia, NOS	9863/3	Other MPN, 9800/3, 9860/3, 9876/3, 9945/3, 9946/3, 9975/3	AML, 9811/3–9818/3, 9835/3–9837/3, 9801/3–9809/3

Chronic myeloid leukaemia, BCR-ABL1 positive	9875/3	Other MPN, 9800/3, 9860/3	AML, 9811/3–9818/3, 9835/3–9837/3, 9801/3–9809/3	
Polycythaemia vera	9950/3	Other MPN	MDS, AML, 9801/3–9809/3	
Myeloproliferative neoplasm, NOS	9960/3	Other MPN, MD/MPN	MDS, AML, 9801/3–9809/3	
Primary myelofibrosis	9961/3	Other MPN, 9931/3	AML (excl 9931), 9801/3–9809/3	
Essential thrombocytaemia	9962/3	Other MPN	MDS, AML, 9801/3–9809/3	
Chronic neutrophilic leukaemia	9963/3	Other MPN, 9800/3, 9860/3	AML, 9801/3–9809/3	
Chronic eosinophilic leukaemia, NOS	9964/3	Other MPN, 9800/3, 9860/3,9965/3, 9966/3, 9967/3	AML, 9801/3–9809/3	
Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1 (MNLE)	Myeloid and lymphoid neoplasms with PDGFRA rearrangement	**9965/3**	MPN, 9800/3, 9820/3, 9860/3, 9964/3,	AML, 9801/3–9809/3
	Myeloid neoplasms with PDGFRB rearrangement	**9966/3**	MPN, 9800/3, 9820/3, 9860/3, 9964/3,	AML, 9801/3–9809/3
	Myeloid and lymphoid neoplasms with FGFR1 rearrangement	**9967/3**	MPN, PLN, 9800/3, 9820/3, 9860/3, 9964/3	AML, 9801/3–9809/3
Myelodysplastic/myeloproliferative neoplasms (MD/MPN)	Atypical chronic myeloid leukaemia, BCR-ABL1 negative	9876/3	Other MD/MPN, MDS, MPN; 9800/3, 9860/3, 9863/3, 9960/3	AML, 9801/3–9809/3
	Chronic myelomonocytic leukaemia	9945/3	Other MD/MPN, MDS, 9800/3, 9860/3, 9863/3, 9960/3	AML, 9801/3–9809/3
	Juvenile myelomonocytic leukaemia	9946/3	Other MD/MPN, MDS, 9800/3, 9860/3, 9863/3, 9960/3	AML, 9801/3–9809/3
	Myelodysplastic/myeloproliferative neoplasm, unclassifiable	**9975/3**	Other MD/MPN, MDS, MPN	AML, 9801/3–9809/3
Myelodysplastic syndromes (MDS)	Refractory anaemia	9980/3	Other MDS, 9945/3, 9975/3	AML, 9801/3, 9860/3
	Refractory anaemia with ring sideroblasts	9982/3	Other MDS, 9945/3, 9975/3	AML, 9801/3, 9860/3
	Refractory anaemia with excess blasts	9983/3	Other MDS, 9945/3, 9975/3	AML, 9801/3, 9860/3
	Refractory cytopenia with multi-lineage dysplasia; Refractory cytopenia of childhood	9985/3	Other MDS, 9945/3, 9975/3	AML, 9801/3, 9860/3
	Myelodysplastic syndrome associated with isolated del(5q)	9986/3	Other MDS, 9945/3, 9975/3	AML, 9801/3, 9860/3
	Myelodysplastic syndrome, NOS	9989/3	Other MDS, MD/MPN	AML, 9801/3, 9860/3
	Refractory neutropenia	**9991/3**	Other MDS, 9945/3, 9975/3	AML, 9801/3, 9860/3
	Refractory thrombocytopenia	**9992/3**	Other MDS, 9945/3, 9975/3	AML, 9801/3, 9860/3
Acute myeloid leukaemia (AML) and related precursor neoplasms.	Blastic plasmacytoid dendritic cell neoplasm (see note 4)	**9727/3**	Other AML, 9800/3–9809/3, 9860/3	
	Acute erythroid leukaemia	9840/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia, NOS	9861/3	Other AML, 9800/3–9809/3, 9860/3, 9965/3, 9966/3, 9967/3	

(*continued on next page*)

Appendix *(continued)*

Major subgroups according to the World Health Organisation (WHO) Classification	Initial diagnosis	Morphology code of the first HM	Major WHO subgroups and morphology codes probably referring to the same tumour as the first HM (see note 3)	Major WHO subgroups and morphology codes referring to potential transformation of the first HM (see note 3)
	Acute myeloid leukaemia with t(6;9)(p23;q34); DEK-NUP214	**9865/3**	Other AML, 9800/3–9809/3, 9860/3	
	Acute promyelocytic leukaemia	9866/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myelomonocytic leukaemia	9867/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1	**9869/3**	Other AML, 9800/3–9809/3, 9860/3	
	Acute basophilic leukaemia	9870/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) CBFB-MYH11	9871/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia with minimal differentiation	9872/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia without maturation	9873/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia with maturation	9874/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute monoblastic and monocytic leukaemia	9891/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia with myelodysplasia-related changes	9895/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia with t(8;21)(q22;q22) RUNX1-RUNX1T1	9896/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia with t(9;11)(p22;q23); MLLT3-MLL	9897/3	Other AML, 9800/3–9809/3, 9860/3	
	Myeloid leukaemia associated with Down Syndrome	**9898/3**	Other AML, 9800/3–9809/3, 9860/3	
	Acute megakaryoblastic leukaemia	9910/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute myeloid leukaemia (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1	**9911/3**	Other AML, 9800/3–9809/3, 9860/3	
	Therapy-related acute myeloid leukaemia	9920/3	Other AML, 9800/3–9809/3, 9860/3; 9987/3	
	Myeloid sarcoma	9930/3	Other AML, 9800/3–9809/3, 9860/3	
	Acute panmyelosis with myelofibrosis	9931/3	Other AML, 9800/3-9809/3, 9860/3, 9961/3	
	Refractory anaemia with excess blasts in transition	9984/3	Other AML, 9800/3-9809/3, 9860/3	
	Therapy-related myelodysplastic syndrome	9987/3	Other AML, MDS	

Precursor lymphoid neoplasms (PLN)	B lymphoblastic lymphoma	9728/3	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	T lymphoblastic lymphoma	9729/3	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9702/3	
	B lymphoblastic leukaemia/lymphoma, NOS	**9811/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1	**9812/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	B lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged	**9813/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)	**9814/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	B lymphoblastic leukaemia/lymphoma with hyperdiploidy	**9815/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	B lymphoblastic leukaemia/lymphoma with hypodiploidy (Hypodiploid ALL)	**9816/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); IL3-IGH	**9817/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)	**9818/3**	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	Lymphoblastic leukaemia/lymphoma, NOS	9835/3	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3, 9702/3	
	B lymphoblastic leukaemia	9836/3	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9826/3, 9680/3, 9684/3, 9687/3	
	T lymphoblastic leukaemia/lymphoma	9837/3	Other PLN, 9590/3, 9591/3, 9800/3-9809/3, 9820/3, 9702/3	
Mature B-cell neoplasms (MBCN), indolent	Primary cutaneous follicle centre lymphoma	**9597/3**	9590/3, 9591/3, 9690/3, 9691/3, 9695/3, 9698/3	
	Small lymphocytic lymphoma	9670/3	9590/3, 9591/3, 9671/3, 9689/3, 9690/3, 9691/3, 9695/3, 9699/3, 9760/3, 9761/3, 9762/3, 9800/3, 9820/3, 9823/3, 9940/3	9680/3, 9650-9655/3, 9661-9667/3
	Chronic lymphocytic leukaemia	9823/3	9590/3, 9591/3, 9670/3, 9671/3, 9689/3, 9690/3, 9691/3, 9695/3, 9699/3, 9800/3, 9820/3, 9940/3	9680/3, 9650-9655/3, 9661-9667/3
	Lymphoplasmacytic lymphoma	9671/3	9590/3, 9591/3, 9670/3, 9760/3, 9761/3, 9762/3, PCN	9680/3, 9650-9655/3, 9661-9667/3
	Waldenström macroglobulinemia	9761/3	9590/3, 9591/3, 9670/3, 9671/3, 9760/3, 9762/3, PCN	9680/3, 9650-9655/3, 9661-9667/3
	Splenic marginal zone lymphoma	9689/3	9590/3, 9591/3, 9670/3, 9699/3	9680/3
	Follicular lymphoma, NOS	9690/3	9590/3, 9591/3, 9597/3, 9670/3, 9691/3, 9695/3, 9698/3	9680/3, 9687/3, 9826/3, 9836/3, 9728/3, 9811/3-9818/3
	Follicular lymphoma, grade 2	9691/3	9590/3, 9591/3, 9597/3, 9670/3, 9690/3, 9695/3, 9698/3	9680/3, 9687/3, 9826/3, 9836/3, 9728/3, 9811/3-9818/3

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Appendix *(continued)*

Major subgroups according to the World Health Organisation (WHO) Classification	Initial diagnosis	Morphology code of the first HM	Major WHO subgroups and morphology codes probably referring to the same tumour as the first HM (see note 3)	Major WHO subgroups and morphology codes referring to potential transformation of the first HM (see note 3)
	Follicular lymphoma, grade 1	9695/3	9590/3, 9591/3, 9597/3, 9670/3, 9690/3, 9691/3, 9698/3	9680/3, 9687/3, 9826/3, 9836/3, 9728/3, 9811/3-9818/3
	Marginal zone lymphoma	9699/3	9590/3, 9591/3, 9670/3, 9689/3	9680/3,
	Heavy chain disease	9762/3	9590/3, 9591/3, 9670/3, 9671/3, 9760/3, 9761/3, PCN	9680/3,
	Immunoproliferative small intestinal disease	9764/3	9590/3, 9591/3,9760/3	9680/3
	Hairy cell leukaemia	9940/3	9590/3, 9591/3, 9670/3, 9800/3, 9820/3, 9823/3	9680/3
Mature B-cell neoplasms (MBCN), aggressive	Mantle cell lymphoma	9673/3	9590/3, 9591/3, 9596/3, 9675/3, 9680/3, 9800/3, 9820/3	
	Primary effusion lymphoma	9678/3	9590/3, 9591/3, 9596/3, 9675/3, 9679/3, 9680/3, 9684/3, 9687/3, 9688/3, 9698/3, 9712/3, 9735/3, 9737/3, 9738/3	
	Primary mediastinal large B-cell lymphoma	9679/3	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9680/3, 9684/3, 9687/3, 9688/3, 9698/3, 9712/3, 9735/3, 9737/3, 9738/3	
	Diffuse large B-cell lymphoma	9680/3	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9684/3, 9687/3, 9688/3, 9698/3, 9712/3, 9735/3, 9737/3, 9738/3	
	Diffuse large B-cell lymphoma, immunoblastic	9684/3	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9680/3, 9687/3, 9688/3, 9698/3, 9712/3, 9735/3, 9737/3, 9738/3	
	Burkitt lymphoma	9687/3	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9680/3, 9684/3, 9688/3, 9698/3, 9800/3, 9801/3, 9820/3, 9826/3, 9712/3, 9735/3, 9737/3, 9738/3, 9835/3	
	T-cell/histiocyte rich large B-cell lymphoma	**9688/3**	9590/3, 9591/3, 9596/3, 9678/3, 9679/3, 9680/3, 9684/3, 9687/3, 9698/3, 9675/3, 9712/3, 9735/3, 9737/3, 9738/3	
	Burkitt leukaemia	9826/3	9590/3, 9591/3, 9596/3, 9678/3, 9679/3, 9680/3, 9684/3, 9687/3, 9688/3, 9800/3, 9801/3, 9805/3-9809/3, 9820/3, 9712/3, 9735/3, 9737/3, 9738/3, 9835/3	
	Follicular lymphoma, grade 3	9698/3	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9680/3, 9684/3, 9687/3, 9688/3, 9690/3, 9691/3, 9695/3, 9712/3, 9735/3, 9737/3, 9738/3, 9597/3	
	Intravascular large B-cell lymphoma (C49.9)	**9712/3**	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9680/3, 9684/3, 9687/3, 9688/3, 9698/3, 9735/3, 9737/3, 9738/3	
	Plasmablastic lymphoma	**9735/3**	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9680/3, 9684/3, 9687/3, 9688/3, 9698/3, 9712/3, 9737/3, 9738/3, PCN	
	ALK positive large B-cell lymphoma	**9737/3**	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9680/3, 9684/3, 9687/3, 9688/3, 9698/3, 9712/3, 9735/3, 9738/3	
	Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease	**9738/3**	9590/3, 9591/3, 9596/3, 9675/3, 9678/3, 9679/3, 9680/3, 9684/3, 9687/3, 9688/3, 9698/3, 9712/3, 9735/3, 9737/3	
	B-cell prolymphocytic leukaemia	9833/3	9590/3, 9591/3, 9800/3, 9820/3, 9823/3, 9832/3	

Mature B-cell neoplasms, plasma cell neoplasms (PCN)	Solitary plasmacytoma of bone	9731/3	9671/3, 9734/3, 9735/3, 9761/3, 9762/3	9732/3; 9733/3
	Plasma cell myeloma	9732/3	9671/3, 9731/3, 9734/3, 9735/3, 9761/3, 9762/3	9733/3
	Plasma cell leukaemia	9733/3	9671/3, 9731/3, 9732/3, 9734/3, 9735/3, 9761/3, 9762/3, 9800/3, 9801/3, 9820/3,	
	Extraosseous plasmacytoma	9734/3	9671/3, 9731/3, 9735/3, 9761/3, 9762/3	9732/3; 9733/3
Mature T-cell and NK-cell neoplasms (MTCN)	Mycosis fungoides	9700/3	Other MTCN (excl. 9702/3), 9590/3, 9591/3	9702/3, 9727/3, 9729/3, 9835/3, 9837/3
	Sézary syndrome	9701/3	Other MTCN, 9590/3, 9591/3	
	(Peripheral) T-cell lymphoma, NOS	9702/3	Other MTCN, 9590/3, 9591/3, 9727/3, 9729/3, 9835/3, 9837/3	
	Angioimmunoblastic T-cell lymphoma	9705/3	Other MTCN, 9590/3, 9591/3	
	Subcutaneous panniculitis-like T-cell lymphoma	9708/3	Other MTCN, 9590/3, 9591/3	
	Cutaneous T-cell lymphoma, NOS	9709/3	Other MTCN (excl. 9702/3), 9590/3, 9591/3	9702/3, 9727/3, 9729/3, 9835/3, 9837/3
	Anaplastic large cell lymphoma, ALK positive	9714/3	Other MTCN, 9590/3, 9591/3	
	Hepatosplenic T-cell lymphoma	9716/3	Other MTCN, 9590/3, 9591/3	
	Enteropathy-associated T-cell lymphoma	9717/3	Other MTCN, 9590/3, 9591/3	
	Primary cutaneous anaplastic large cell lymphoma	9718/3	Other MTCN, 9590/3, 9591/3	
	Extranodal NK/T-cell lymphoma, nasal type	9719/3	Other MTCN, 9590/3, 9591/3	
	Systemic EBV positive T-cell lymphoproliferative disease of childhood	**9724/3**	Other MTCN, 9590/3, 9591/3	
	Hydroavacciniforme-like lymphoma	**9725/3**	Other MTCN, 9590/3, 9591/3	
	Primary cutaneous gamma-delta T-cell lymphoma	**9726/3**	Other MTCN, 9590/3, 9591/3	
	Adult T-cell leukaemia/lymphoma	9827/3	Other MTCN, 9800/3, 9801/3, 9805/3-9809/3, 9820/3	

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Appendix *(continued)*

Major subgroups according to the World Health Organisation (WHO) Classification	Initial diagnosis	Morphology code of the first HM	Major WHO subgroups and morphology codes probably referring to the same tumour as the first HM (see note 3)	Major WHO subgroups and morphology codes referring to potential transformation of the first HM (see note 3)
	T-cell large granular lymphocytic leukaemia	9831/3	Other MTCN, 9590/3, 9591/3, 9800/3, 9820/3, 9832/3	
	T-cell prolymphocytic leukaemia	9834/3	Other MTCN, 9590/3, 9591/3, 9800/3, 9820/3, 9832/3	
	Aggressive NK-cell leukaemia	9948/3	Other MTCN, 9800/3, 9801/3, 9805/3-8909/3, 9820/3	
Hodgkin lymphoma (HL)	Hodgkin lymphoma, NOS	9650/3	Other HL, 9590/3, 9596/3	
	Lymphocyte-rich classical Hodgkin lymphoma	9651/3	Other HL, 9590/3, 9596/3	
	Mixed cellularity classical Hodgkin lymphoma	9652/3	Other HL, 9590/3, 9596/3	
	Lymphocyte-depleted classical Hodgkin lymphoma	9653/3	Other HL, 9590/3, 9596/3	
	Lymphocyte-depleted classical Hodgkin lymphoma, diffuse fibrosis	9654/3	Other HL, 9590/3, 9596/3	
	Lymphocyte-depleted classical Hodgkin lymphoma, reticular	9655/3	Other HL, 9590/3, 9596/3	
	Nodular lymphocyte predominant Hodgkin lymphoma	9659/3	Other HL, 9590/3, 9596/3	9680/3
	Hodgkin granuloma	9661/3	Other HL, 9590/3, 9596/3	
	Hodgkin sarcoma	9662/3	Other HL, 9590/3, 9596/3	
	Nodular sclerosis classical Hodgkin lymphoma	9663/3	Other HL, 9590/3, 9596/3	
	Nodular sclerosis classical Hodgkin lymphoma, cellular phase	9664/3	Other HL, 9590/3, 9596/3	
	Nodular sclerosis classical Hodgkin lymphoma, grade 1	9665/3	Other HL, 9590/3, 9596/3	
	Nodular sclerosis classical Hodgkin lymphoma, grade 2	9667/3	Other HL, 9590/3, 9596/3	
Histiocytic and dendritic cell neoplasms (HDCN)	Malignant histiocytosis, NOS	9750/3	Other HDCN	
	Langerhans cell histiocytosis	9751/3	Other HDCN	
	Langerhans cell histiocytosis, unifocal	9752/1	Other HDCN (see note 2)	
	Langerhans cell histiocytosis, multifocal	9753/1	Other HDCN (see note 2)	

	Langerhans cell histiocytosis, disseminated	9754/3	Other HDCN (see note 2)
	Histiocytic sarcoma	9755/3	Other HDCN
	Langerhans cell sarcoma	9756/3	Other HDCN
	Interdigitating dendritic cell sarcoma; intermediate dendritic cell tumour	9757/3	Other HDCN
	Follicular dendritic cell tumour	9758/3	Other HDCN
	Fibroblastic reticular cell tumour	**9759/3**	Other HDCN
Unspecified/mixed neoplasms	Lymphoma, NOS	9590/3	HL, MBCN, MTCN, PLN, 9591/3, 9596/3, 9760/3
	Non-Hodgkin lymphoma, NOS	9591/3	MBCN, MTCN, PLN, 9590/3, 9596/3,9760/3
	Mixed Hodgkin lymphoma and non-Hodgkin lymphoma	9596/3	HL, MBCN, MTCN, PLN, 9590/3, 9591/3
	Malignant lymphoma, mixed small and large cell, diffuse	9675/3	MBCN, MTCN, PLN, 9590/3, 9591/3
	Immunoproliferative disease, NOS	9760/3	MBCN, 9590/3, 9591/3
	Leukaemia, NOS	9800/3	9670/3, 9673/3, 9733/3, 9742/3, 9801/3-9948/3, 9963, 9964, 9965/3, 9966/3, 9967/3
	Acute undifferentiated leukaemia; acute leukaemia, NOS	9801/3	9733/3, 9800/3, 9805/3, 9806/3, 9807/3, 9808/3, 9809/3, 9820/3, 9826/3, 9827/3, , 9948/3, 9965/3 9966/3, PLN, AML
	Mixed phenotype acute leukaemia, NOS	9805/3	9800/3, 9801/3, 9806/3, 9807/3, 9808/3, 9809/3, 9820/3, 9826/3, 9827/3, 9860/3, , 9948/3, PLN, AML
	Mixed phenotype acute leukaemia with t(9;22)(q34;q11.2); BCR-ABL1	**9806/3**	9800/3, 9801/3, 9805/3, 9807/3, 9808/3, 9809/3, 9820/3, 9826/3, 9827/3, , 9948/3, PLN, AML
	Mixed phenotype acute leukaemia with t(v;11q23); MLL rearranged	**9807/3**	9800/3, 9801/3, 9805/3, 9806/3, 9808/3, 9809/3, 9820/3, 9826/3, 9827/3, 9948/3, PLN, AML
	Mixed phenotype acute leukaemia, B/myeloid, NOS	**9808/3**	9800/3, 9801/3, 9805/3, 9806/3, 9807/3, 9809/3, 9820/3, 9826/3, 9827/3, 9948/3, PLN, AML
	Mixed phenotype acute leukaemia, T/myeloid, NOS	**9809/3**	9800/3, 9801/3, 9805/3, 9806/3, 9807/3, 9808/3, 9820/3, 9826/3, 9827/3, 9948/3, PLN, AML
	Lymphocytic leukaemia, NOS	9820/3	9670/3, 9673/3, 9733/3, 9800/3, 9801/3, 9805/3-9809/3, 9823/3-9834/3, 9940/3, 9965/3, 9966/3, 9967/3, PLN
	Prolymphocytic leukaemia, NOS	9832/3	9800/3, 9820/3, 9833/3, 9834/3
	Myeloid leukaemia, NOS	9860/3	9742/3, 9800/3, 9801/3, 9805/3, 9840/3-9931/3, 9945/3, 9946/3, 9963/3, 9964/3, 9965/3, 9966/3, 9967/3

Note 1. In systemic mastocytosis (SM) a coexisting haematological neoplasm may be present (SM-AHNMD). Then, the disease meets the criteria for SM and the criteria for an associated, clonal haematological non-mast cell lineage disorder (MDS, MPN, AML, lymphoma or other haematological neoplasm that meet the criteria for a distinct entity in the WHO classification). This may progress/transform to acute leukaemia.

Note 2. Langerhans cell histiocytosis, irrespective of the degree of dissemination, was reclassified from /1 to /3 in the 4th edition of the WHO Classification.

Note 3. Even if the morphology codes mentioned in this table refer to the same tumour or to a transformation, there may be clinical evidence for a second tumour. In those (often rare) cases two tumours should be registered. For example, if a patient has a diagnosis of myeloma and a diagnosis of lymphoplasmocytic lymphoma, they may be considered as one disease, but they may also be two different diseases if there is clinical evidence for the latter, based on the type of immunoglobulins.

Note 4. Morphology code 9727 was used for 'Precursor cell lymphoblastic lymphoma, NOS' in ICD-O-3, while according to the 2011 ICD-O-3 Update this morphology code is used for 'Blastic plasmocytoid dendritic cell neoplasm.

References

[1] Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H et al. European cancer observatory: cancer incidence, mortality, prevalence and survival in Europe. Version 1.0 European Network of Cancer Registries, International Agency for Research on Cancer [Internet]. Available from: http://eco.iarc.fr. [September 2012 accessed on 18 September 2013].

[2] Lin YW, Aplan PD. Leukemic transformation. Cancer Biol Ther 2004;3(1):13–20 [Epub 2004 Jan 8].

[3] Fritz A, Percy C, Jack A, editors. International classification of diseases for oncology. Geneva: World Health Organisation; 2000.

[4] Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissue. Geneva: World Health Organisation; 2008.

[5] International Agency for Research on Cancer and World Health Organization. 2011 Updates to ICD-O-3 [Internet]; 2011. Available from: http://www.who.int/classifications/icd/updates/icd03updates/en/index.html.

[6] Sant M, Karjalianen-Lindsberg ML, Maynadié M, Raphaël M, Ferretti S, Giacomin A et al., editors. Manual for coding and reporting haematological malignancies [Internet]. 2010 Available from: http://www.tumorionline.it/pdf/HAEMACARE.pdf.

[7] European Network of Cancer Registries. Recommendations issued by ENCR. Available from: http://www.encr.eu/index.php/activities/recommendations.

[8] Surveillance, Epidemiology, and End Results Program. Hematopoietic and Lymphoid Neoplasm Database [Internet]; 2013. Available from: http://seer.cancer.gov/seertools/hemelymph/.

[9] Tyczynski JE, Démaret E, Parkin DM. Standards and guidelines for cancer registration in Europe. The ENCR Recommendations, Volume 1. IARC Technical Publication No 40. Also available from http://www.encr.com.fr/incideng.pdf.

[10] Heinävaara S, Teppo L, Hakulinen T. Cancer-specific survival of patients with multiple cancers: an application to patients with multiple breast cancers. Stat Med 2002;21:3183–95.

[11] Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, editors. Cancer incidence in five continents, vol. IX. Lyon: IARC Scientific Publications No. 160; 2007.

[12] International Agency for Research on Cancer. CI5 X [Internet]. 2013. Available from: http://ci5.iarc.fr/CI5-X/ci5-X.htm.