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## Manual for Coding and Reporting Haematological Malignancies

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## Preface

The large variation in registration and codification procedures for haematological malignancies greatly complicates comparisons of survival, incidence and prevalence. To address this problem the HAEMACARE expert panel decided to promulgate standard rules for the registration of such malignancies for use by population-based cancer registries. Twelve experts (senior physicians, epidemiologists and onco-haematologists) from France, Finland, Italy, Spain, Switzerland, and The Netherlands, worked together to prepare this coding and reporting manual for haematological malignancies, that integrates and summarises experience with existing manuals used in various countries.

This manual is mainly based on the recommendations of the WHO's International Classification of Diseases in Oncology, 3rd edition 2000; the Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2001 and 2008; the European Network of Cancer Registries (ENCR); the French Network of Cancer Registries (FRANCIM) manual; and the Italian Association of Cancer Registries (AIRTUM) manual.

Haematological malignancies are classified into two main categories based on cell lineage – myeloid and lymphoid. Within each of these groups, malignancies are further sub-divided according to cell of origin, morphology, immunohistochemistry, genetic characteristics, and clinical behaviour.

Each subcategory is likely to have a distinct physiopathology and prognosis. It is for this reason that the HAEMACARE panel also worked to develop a consensus grouping of all ICD-O-3 morphology codes into groups of similar physiopathology and prognosis, useful for incidence and survival analyses. This grouping is consistent with that elaborated by INTERLYMPH and is reproduced at the end of this manual. In the HAEMACARE grouping the main subgroups are identified by colours. Within these subgroups, further subdivisions are indicated by different shades. Cancer registries are encouraged to make use of this grouping of morphology codes in their incidence and survival studies.

## List of abbreviations

AIRTUM	Italian association of cancer registries
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoid/lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ATLL	Adult T-cell leukaemia/lymphoma
B-ALL	Precursor B-cell lymphoblastic leukaemia
B-PLL	Prolymphocytic leukaemia B-cell type
CHL	Classical Hodgkin lymphoma
CLL/PL	Chronic lymphocytic leukaemia with increased prolymphocytes
CLL/SLL	Chronic lymphocytic leukaemia/small lymphocytic lymphoma
CML	Chronic myeloid leukaemia
CML BP	Chronic myeloid leukaemia blast phase
CMMML	Chronic myelomonocytic leukaemia
CMPN	Chronic myeloproliferative neoplasm
CNS	Central nervous system
CRAB	Hypercalcaemia, renal insufficiency, anaemia, bone lesions
DCO	Death certificate only
ENCR	European network of cancer registries
ETO	Eight-twenty-one corepressor
FAB classification	French-American-British classification
FRANCIM	French network of cancer registries
GM-CSF	Granulocyte macrophage colony stimulating factor
HHV	Human herpes virus
HL	Hodgkin lymphoma
HM	Haematological malignancies
ICD-O-3	International classification of diseases for Oncology (Third edition)
HTLV 1	Human T-lymphotropic virus
INTERLYMPH	International lymphoma epidemiology consortium
IPSID	Immunoproliferative small intestinal disease
JMML	Juvenile myelomonocytic leukaemia
KSHV	Kaposi sarcoma herpes virus
LDHL	Lymphocyte depleted Hodgkin lymphoma
LPL/WM	Lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia
LRCHL	Lymphocyte rich classical Hodgkin lymphoma
MALT	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue
MCHL	Mixed cellularity Hodgkin lymphoma
MCL	Mast cell leukaemia
MDS	Myelodysplastic syndrome
MF	Mycosis fungoides
MGUS	Monoclonal gammopathy of undetermined significance
MPN	Myeloproliferative neoplasms
NH	Non Hodgkin
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
NOS	Not otherwise specified
NSHL	Nodular sclerosis Hodgkin lymphoma
RAEB	Refractory anaemia with excess blasts in transformation
RARS	Refractory anaemia with ringed sideroblasts
REAL	Revised European-American classification of lymphoid neoplasms
SS	Sézary syndrome
TCRs	T-cell receptors
T-LGL	T-cell large granular lymphocytic leukaemia
WHO	World Health Organization

# 1. Introduction

Haematological malignancies (HMs) 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 malignant and aggressive, or transform into a different tumour type. The transformed cells proliferate excessively or are resistant to apoptosis. Factors such as viral infection, immunological disturbances, exposure to cytotoxic or immunosuppressive drugs, and organ transplantation may all influence the development of a HM. HMs may be diagnosed at any stage in the process of malignant transformation.

HMs are generally multisystem diseases and can be classified using various criteria (location, morphology, immunophenotype, genetic features, clinical features, lineage, etc), complicating classification and also diagnosis.

Better understanding of natural history of these diseases, together with rapid advances in methods for diagnosis and prognosis prediction, and the development

of targeted therapies, have led to improvement in both HM classification and therapeutic outcomes.

## **Aim of this Manual**

This manual is intended to be practical aid to people working in European cancer registries.

Its specific objectives are:

1. To provide recommendations for the collection of information on HMs.
2. To set out standardized rules for coding HMs.
3. To present detailed practical instructions for the registration and coding of HMs.

It is hoped as the dissemination and wide use of this manual will improve the consistency and homogeneity of HM registration and coding by European cancer registries and thereby improve the comparability of incidence and survival data for HMs across European cancer registries.

## 2. General recommendations

### 2.1. Incidence date

The rules of the European Network of Cancer Registries<sup>1</sup> must be followed in assigning the date of incidence of an HM for the purposes of cancer registration. These rules are as follows:

Of the six events listed below (whose dates may be available to a cancer registry) the date assigned as the incidence date must be the date of the event that occurs highest in the list. If the date an event higher in the list becomes available within three months of the date initially assigned, then that date should substitute the date originally chosen.

Events in order of priority:

1. First histological or cytological confirmation of malignancy (except histological or cytological confirmation at autopsy). Sub-priorities are as follows:
  - a. Date the biopsy was taken
  - b. Date of receipt of biopsy specimen by pathologist (or pathological lab)
  - c. Date of pathological report
2. Admission to hospital pertaining to current malignancy
3. If patient seen at an outpatient clinic only: date of first visit to outpatient clinic for the current malignancy
4. A diagnosis arising other than by 1, 2 or 3 above
5. Death, if no information is available other than the fact that the patient has died of a malignancy
6. Death, if malignancy is discovered at autopsy

Whatever incidence date is selected, it cannot be later than the date of the start of treatment, or the date of the decision not to treat, or the date of death.

The date of incidence has no influence on the “Basis of diagnosis” coding (Section 2.3).

When several examinations are required to obtain a diagnosis, the incidence date is the date of confirmation of malignancy.

### 2.2. Sources of haematological data

While in theory the information sources for HMs are the same as those for solid tumours, the following specific sources are particularly important:

- Haematology/oncology units, including paediatric oncology units
- Laboratories performing biological tests and investi-

gations (pathology, haematology, immunology, genetic and molecular)

- Clinical records, hospital discharge records
- General practitioners and haematological outpatient care centres

Haematology/oncology units in public and private hospitals are major sources of information on HMs. Haematology and pathology labs are also fundamental, since they perform morphological and immunophenotypic analyses of peripheral blood and bone marrow samples, allowing the diagnosis of various HMs and premalignant lesions.

Centres performing cytogenetic and molecular analyses provide essential information about HM subtypes. For example, cytogenetic analysis is essential for establishing the diagnosis of acute myeloid leukaemia (AML), myelodysplastic syndromes (MDS) and chronic myeloid leukaemia (CML), and for identifying other myeloproliferative and lymphoproliferative disorders [e.g., JAK-2 mutation to confirm polycythaemia vera, t(11; 14) translocation to confirm mantle cell lymphoma, or t(8;14) transition to confirm Burkitt's lymphoma].

Clinical records and hospital discharges are additional important sources of information, while general practitioners and haematological outpatient centres treat patients with myelodysplastic syndromes, myeloproliferative diseases, and chronic lymphoid diseases and hence are valuable sources of information on patients with these conditions.

### 2.3. Basis of diagnosis

The basis of diagnosis follows the ENCR recommendations<sup>1,2</sup>. A code should be assigned to each case indicating the basis of diagnosis. The codes are hierarchical, with higher numbers (except code 9) indicating a more secure basis for the diagnosis than lower numbers. The highest available code should always be assigned. If basis of diagnosis information is not available (information obtained from an automated source, for example) code 9 (Unknown) should be assigned. Cases coded 9 are excluded from calculations of percentages of cases diagnosed clinically, microscopically, by death certificate only, etc.

In general, codes 5 and 7 are most appropriate for HMs, and codes 1, 2 or 4 should not be used; however code 4 may be applicable to multiple myeloma without microscopic verification and code 2 may be applicable to brain lymphoma.



**Table 2.3.1. - Recommendations for basis-of-diagnosis codes**

Code	Basis of diagnosis	Comment
0	Death certificate only	The only source of information is a death certificate
Non-microscopic		
1	Physical examination	Diagnosis made before death, but without the support of diagnostic modalities 2-7 below
2	Instrumental/surgical examination	Diagnosis based on results of instrumental or surgical examinations, including X-ray, endoscopy, imaging, ultrasound, exploratory surgery (e.g., laparotomy) or autopsy, but without cytological or histological examination
4	Specific tumour marker	Diagnosis based on determination of biochemical or immunological markers specific for a tumour – for multiple myeloma: high serum immunoglobulins (IgG >35 g/L or IgA >20 g/L or high light chain urinary excretion >1g/24 hr); – for Waldenström macroglobulinaemia: IgM >10 g/L <sup>3</sup>
Microscopic		
5	Cytological examination of peripheral blood, bone marrow aspirate, or other aspirates	Diagnosis based on microscopic examination of peripheral blood films, bone marrow aspirates, or cells aspirated from a primary or secondary site
6	Histology of metastasis	Not applicable to haematological malignancies
7	Histology of tissue	Lymph node or tissue biopsy including trephine bone marrow biopsy
9	Unknown	

## 3. Coding rules

### 3.1. ICD-O-3 classification

The International Classification of Diseases for Oncology, 3<sup>rd</sup> revision (ICD-O-3) and WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2008 (which is based on ICD-O-3) are the main sources for the HM classification and coding presented in this Manual<sup>4, 5</sup>.

Note that the category *non-Hodgkin lymphoma* is not a formal classification category in the ICD-O-3 or WHO publications, and is occasionally used in the present Manual although, again as an informal term<sup>4, 5</sup>.

Note the following differences between the ICD-O-3 and the WHO classifications:

- Lymphoid papulosis is coded as 9718/3 by ICD-O-3 and 9718/1 by the WHO 2008. It is recommended that this entity not be registered as it is now considered benign.
- T-cell large granular lymphocytic leukaemia is coded as 9831/1 by ICD-O-3 and 9831/3 by the WHO 2008. It should be registered as malign in accord with the WHO code.
- Not otherwise specified (NOS) myelodysplastic/myeloproliferative syndrome is not coded in ICD-O-3, but is 9975/3 in WHO, and should therefore be registered.

### 3.2. Natural history of haematological malignancies

Various malignant and non-malignant haematological entities can transform into different HM entities. For example, myelodysplastic syndrome or myeloproliferative neoplasm can transform into acute leukaemia, and Waldenström macroglobulinaemia can transform into lymphoplasmocytic lymphoma.

### 3.2.1. Transformation

If a malignant HM (behaviour /3) occurs after a different, previously diagnosed, malignant HM in a given patient, the second HM should be considered as a transformation of the first, and should be coded as a transformed HM. To accommodate the possibility of such transformations the following additional items should be included in the cancer registry database.

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

### 3.2.2. New tumour

If a malignant HM (behaviour /3) occurs after a previous non-malignant HM (behaviour code /1), the former should be registered as a new tumour and the patient has multiple tumour (Section 3.3).

### 3.3. Multiple tumours and transformed tumours

An HM occurring after a first tumour must be considered as a transformation of the first if it has the same cell lineage (e.g., both lymphoid malignancies). If the cell lineage of the second HM is different from that of the first, we are dealing with multiple tumours (e.g., a myeloid HM follows a lymphoid HM). In this case the international rules (ICD-O-3 and ENCR recommendations) for multiple primary cancers must be used for registration<sup>1,4</sup>. An exception is chronic myeloid leukaemia in blast phase (CML-BP) which can transform into acute myeloid leukaemia (AML) or into acute lymphoid leukaemia (ALL).

Table 3.3.1. illustrates transformation possibilities for

**Table 3.3.1. - Examples of HMs transformations with morphologic codes**

HM	ICD-O-3 morphological codes of transformations
Myeloid	9840, 9861-9931, 9945-9946, 9950, 9961-9964, 9980-9987
B-cell neoplasms	9670-9699, 9728, 9731-9734, 9761-9767, 9769, 9823-9826, 9833, 9836, 9940
T-cell and NK-cell neoplasms	9700-9719, 9729, 9768, 9827-9831, 9834, 9837, 9948
Hodgkin lymphoma	9650-9667
Mast cell tumour	9740-9742
Histiocytic or accessory lymphoid cell neoplasms	9750-9758
Unspecified types	9590-9591, 9596, 9727, 9760, 9800-9801, 9805, 9820, 9832, 9835, 9860, 9960, 9970, 9975, 9989

some HMs. The HM in the left column can transform into (one of) the entities whose ICD-O-3 morphology codes are listed in the same row of the right column.

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 considered as a new tumour and not registered as incident.

When a pathological specimen/slide is reviewed by a second pathologist, the second opinion is considered the definitive diagnosis, but date of incidence remains that of the first HM.

If the diagnosis on the death certificate does not agree with the diagnosis on pathological reports, the date of

pathological diagnosis (pathological report) must be registered as the date of diagnosis.

### Transformations from premalignant lesions

Premalignant conditions are registered by some registries. However these cases must not be included in incidence series. If a premalignant lesion transforms into a malignant HM, the transformed disease should be included in incidence data, and its date of incidence is the date of transformation from the premalignant condition.

**Table 3.3.2. - Recommendations for distinguishing between transformations and multiple tumours<sup>6</sup>**

Initial diagnosis	Subsequent diagnosis	Recommendation
Nodal lymphoma	Extranodal lymphoma	Only consider as multiple tumour if the cell lines differ (e.g., B cell vs. T-cell; B cell vs. NK cell; B cell vs. null cell)
Low grade non-Hodgkin lymphoma	High grade non-Hodgkin lymphoma	Only consider as multiple tumour if the cell lines differ (B cell vs. T-cell; B cell vs. NK cell; B cell vs. null cell)
High grade non-Hodgkin lymphoma	Acute lymphoblastic leukaemia	Do not register as multiple tumour, but as transformation
Chronic lymphocytic leukaemia	High grade non-Hodgkin lymphoma (Richter syndrome)	Only consider as multiple tumour if the cell lines differ (e.g., B cell vs. T-cell; B cell vs. NK cell; B cell vs. null cell)
Chronic lymphocytic leukaemia	Hodgkin lymphoma	Multiple tumour
Chronic lymphocytic leukaemia	Acute lymphoid leukaemia	Transformation
Non-Hodgkin lymphoma	Hodgkin lymphoma	Multiple tumour
Hodgkin lymphoma	Non-Hodgkin lymphoma	Multiple tumour
Hodgkin lymphoma	Acute myeloid leukaemia	Multiple tumour
Hodgkin lymphoma	Myelodysplastic syndrome	Multiple tumour
Chronic myeloid leukaemia	Acute myeloid leukaemia	Transformation
Chronic myeloid leukaemia	Acute lymphoid leukaemia	Transformation
Myeloid leukaemia	Myelodysplastic syndrome (MDS)	Transformation. Do not register as multiple tumour if MDS is considered secondary to therapy
Myelodysplastic syndrome	Acute myeloid leukaemia	Transformation
Lymphocytic leukaemia/lymphoma	Myelodysplastic syndrome	Multiple tumour
Chronic myelomonocytic leukaemia	Acute myeloid leukaemia	Transformation
Chronic myelomonocytic leukaemia	Myelodysplastic syndrome	Transformation
Polycythaemia vera	Acute myeloid leukaemia	Transformation
Essential thrombocythaemia	Acute myeloid leukaemia	Transformation
Multiple myeloma	Acute myeloid leukaemia	Multiple tumour
Multiple myeloma	Non-Hodgkin lymphoma	Transformation
Waldenström macroglobulinaemia	Non-Hodgkin lymphoma	Transformation
Polycythaemia vera	Primary myelofibrosis	Transformation
Essential thrombocythaemia	Primary myelofibrosis	Transformation

### 3.4. Forbidden HM codes

- A topography C80.9 corresponding to a solid tumour is not allowed for HM.
- Morphologies 9765/1, 9766/1, 9767/1, 9768/1, 9769/1, 9751/1, 9752/1, and 9753/1 refer to non-malignant immunoproliferative diseases and are not registered.

### 3.5. Obsolete codes, not to be used

- 9654/3 (Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis) and 9655/3 (Hodgkin lymphoma lymphocyte depletion reticular) must both be coded as 9653/3 (Hodgkin lymphoma lymphocyte depletion NOS).
- 9661/3 (Hodgkin granuloma) and 9662/3 (Hodgkin sarcoma) must both be coded as 9650/3.
- 9664/3 (Hodgkin lymphoma, nodular sclerosis, cellular phase), 9665/3 (Hodgkin lymphoma nodular sclerosis grade 1), and 9667/3 (Hodgkin lymphoma nodu-

lar sclerosis grade 2) must all now be coded as 9663/3 (Hodgkin lymphoma nodular sclerosis, NOS).

- 9590/3 (malignant lymphoma, NOS) must be avoided wherever possible. More information should be actively sought in order to establish the cell lineage.
- 9800-3 (leukaemia NOS), 9820-3 (Lymphoid leukaemia NOS), and 9860-3 (myeloid leukaemia NOS) must be avoided wherever possible, and more information should be actively sought in order to obtain a more specific disease characterization.

### 3.6. Updated codes for HMs (from 2008 WHO classification)<sup>5</sup>

- Mastocytomas (9740/1 or /3) are now considered as myeloproliferative neoplasms.
- Angioimmunoblastic lymphadenopathy (9767/1) is now considered angioimmunoblastic T-cell lymphoma and should be coded as 9705/3.

## 4. Myeloid malignancies

### 4.1. Acute leukaemia

#### Definition

Acute leukaemias are proliferations of immature hematopoietic cells (blasts) initially in bone marrow, subsequently in peripheral blood, and eventually in most organs. Acute leukaemias are classified according to lineage: acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML) or less frequently biphenotypic, when the malignant cells show markers for the myeloid and lymphoid lineages, or the B and T-cell markers in the lymphoid lineage.

#### Coding rules

- **Topography**  
For acute leukaemias, the topography is always C42.1 (bone marrow), even though locations other than bone marrow may be evident (skin, CNS, spleen, etc.).
- **Morphology**  
The code for leukaemia (9800/3) should never be used, unless no other information is available [a death certificate only (DCO) case]. It is important to actively search for additional information in the presence of a DCO case: such information can almost always be found.
- **Consensus coding/incidence rules regarding transformations into acute leukaemia**
  - a. If an acute leukaemia derives from a transformation of a previously diagnosed HM, the first HM is considered the incident disease (not the AL), and the date of incidence is that of the first HM diagnosis.
  - b. If the acute leukaemia was diagnosed less than 3 months after the diagnosis of a myelodysplastic syndrome (MDS) or a chronic myeloproliferative neoplasm (CMPN), then only acute leukaemia should be registered. The date of incidence is the date of diagnosis of the MDS or CMPN.  
If the period between the two diagnoses is more than 3 months, the acute leukaemia must be coded as a transformation.
  - c. If acute leukaemia is diagnosed in a patient known to have MDS or a CMPN, the MDS or CMPN must be registered, and the acute leukaemia must only be registered as a transformation. If the incidence date of the MDS or CMPN is unknown, use ENCR rules to find an approximate date of incidence<sup>1,2</sup>.
  - d. If an acute leukaemia diagnosis is accompanied by a note or comment that it could be secondary to an unknown (not diagnosed) MDS or a CMPN, only acute leukaemia is registered.

- **Bone marrow examination not available**

Rarely the result of bone marrow examination is not available and the acute leukaemia diagnosis is based on examination of peripheral blood only. The presence of blasts ( $\geq 20\%$ ) in blood is sufficient to secure the diagnosis of acute leukaemia. In such cases ICD-O-3 code 9801/3 (acute leukaemia) and not 9800/3 (leukaemia) must be used. The diagnosis can be made more precise if myeloperoxidase staining or immunophenotype was performed. It is then possible to distinguish ALL from AML, and B-cell ALL from T-cell ALL. If karyotypic or molecular analyses were performed, the diagnosis of AML with recurrent genetic abnormalities may be possible. Note, however, that it is impossible to further refine the AML diagnosis in the absence of information from bone marrow.

#### Other coding rules

- a. When a granulocytic sarcoma (chloroma) is diagnosed, the bone marrow aspirate/biopsy report must be checked:
  - if there is bone marrow proliferation, this must be coded first
  - if the bone marrow is normal, code 9930/3 (granulocytic sarcoma)
  - if bone marrow was not evaluated, code 9861/3 (AML, NOS), based on blood examination and clinical data.
- b. The code 9860/3 (myeloid leukaemia, NOS) should be avoided and efforts should be made in order to reach a better disease definition.
- c. Eosinophilic leukaemia must be coded as 9964/3 (chronic eosinophilic leukaemia).
- d. For promyelocytic leukaemia [with t(15;17) translocation or variant] and for acute myelomonocytic leukaemia with eosinophils [inv(16), t(16;16)], which are classified as AMLs with recurrent cytogenetic abnormalities, cytogenetic evaluations are not mandatory as cytological features are sufficient to secure the diagnosis.

#### Additional comments

- According to ICD-O-3, the diagnosis of acute leukaemia requires the presence of karyotypic abnormalities or of molecular hallmarks. If the results of these examinations are not available, they must be systematically searched for using the resources available to the cancer registry. If after searching this information is still not available, the codes of older French-American-British (FAB) classification should be used. Note: karyotypic and molecular analyses are performed repeatedly during the disease course.

However the only acceptable results for diagnostic purposes are those performed before treatment, so particular care should be taken to check the dates of all examinations, and use only the examination result obtained before treatment.

- For the diagnosis of acute leukaemia, priority is given to the result of the bone marrow aspirate even if both bone marrow aspirate and bone marrow biopsy are available.
- For the diagnosis of acute leukaemia, if the cytochemical and immunophenotypic examinations are not concordant, priority is given to the results of the immunophenotypic examination.

If an acute leukaemia diagnosis is given in the clinical record, based only on the finding of  $\geq 20\%$  blast cells in peripheral blood (i.e., absence of marrow aspirate or biopsy) the clinical diagnosis made by the clinician should be retained.

- The term *sub acute* is obsolete. When it appears in a report, check the bone marrow smear and apply the following criteria:
  - $\geq 20\%$  blasts in bone marrow: acute leukaemia;
  - $< 20\%$  blast in bone marrow: chronic leukaemia, MDS, or CMPN.
- The term *secondary* is ambiguous: it could mean secondary to a previous condition (such as MDS or CMPN), or secondary to cytotoxic therapy (chemotherapy or radiotherapy). It is important to review all the information available to ascertain the precise meaning. In general:

- if the leukaemia develops in the absence of cytotoxic therapy (“as part of the natural history of a disease”) it should be coded as a transformation;
- if the leukaemia develops after a patient has received cytotoxic therapy, it should be coded as 9920/3 (if an AML, as *acute myeloid leukaemia secondary to treatment*).

#### 4.1.1. Acute myeloblastic leukaemia

##### Main diagnostic criteria

- **Bone marrow aspirate/biopsy  $\geq 20\%$  blasts (peroxidase  $> 3\%$ )**  
In exceptional situations, bone marrow is not evaluated but the diagnosis of leukaemia can be made if peripheral blood contains  $\geq 20\%$  blasts.
- **Immunophenotyping** positive myeloid markers: CD11c, CD13, CD14, CD15, CD33, CD117.
- **Myeloperoxidase**  $> 10\%$ .

##### Classification

In the WHO classification of 2008<sup>5</sup> acute myeloblastic leukaemias (AMLs) are divided into four hierarchical groups (the first taking precedence over the second, the second over the third, etc., for coding purposes). Cytogenetic features and previous chemotherapy/radiotherapy are necessary to assign the category and should always be checked. The code for the fourth group is assigned only if the case does not fit any of the three previous categories.

**Table 4.1.1.1. - WHO classification of AMLs<sup>5</sup>**

Group	Characteristics	Diagnosis	ICD-O-3 code
I	AML with recurrent cytogenetic abnormalities	AML with t(8;21) or positive AML1/ETO	9896/3
		Promyelocytic AML [t(15 ;17) and variants]	9866/3
		AML with inv(16), or t(16 ;16)	9871/3
		AML with 11q23 abnormalities	9897/3
II	AML with multilineage dysplasia, with or without previous myelodysplastic syndrome, $\geq 20\%$ blasts in bone marrow and dysplasia in $\geq 50\%$ of cells in at least two lineages	AML with multilineage dysplasia	9895/3
III	AML after prior chemotherapy or radio therapy	Therapy-related AML	9920/3
IV	AMLs that do not fit in the above groups and that can be characterized by only cytological or immunophenotypic features	Minimally differentiated AML (M0)	9872/3
		AML without maturation (M1)	9873/3
		AML with maturation (M2)	9874/3
		Acute myelomonocytic leukaemia (M4)	9867/3
		Acute monoblastic/monocytic leukaemia (M5)	9891/3
		Acute erythroid leukaemia (M6)	9840/3
		includes erythroleukaemia (erythroid/myeloid) and pure erythroid leukaemia	
		Acute megakaryoblastic leukaemia (M7)	9910/3
		includes AML/transient myeloproliferative disorder in Down syndrome	
Acute basophilic leukaemia	9870/3		
Acute panmyelosis with myelofibrosis	9931/3		
Myeloid sarcoma (chloroma, granulocytic sarcoma)	9930/3		



**4.1.2. Acute leukaemias of ambiguous lineage**

*Definition*

Acute leukaemias of ambiguous lineage are proliferations of immature hematopoietic cells (blast cells) expressing markers characteristic of two lineages (myeloid and lymphoid; or B-cell and T-cell markers in lymphoid lineage), initially in bone marrow.

Acute leukaemias of ambiguous lineage comprise:

- Bilineage leukaemia, with two distinct blast populations, one expressing myeloid markers the other expressing lymphoid markers.
- Undifferentiated leukaemia, when immunophenotypic analysis does not provide evidence to decide whether the proliferation is of myeloid or lymphoid origin.
- Biphenotypic leukaemia in which all blast cells express myeloid and lymphoid markers according to the European Group for Immunology of Leukaemia score<sup>5</sup>.

**Table 4.1.2.1. - Codes for acute leukaemias of ambiguous lineage**

Diagnosis	ICD-O-3 code
Acute biphenotypic leukaemia Acute mixed lineage leukaemia Acute bilinear leukaemia	9805/3
Acute leukaemia, NOS Acute undifferentiated leukaemia, NOS Stem cell leukaemia	9801/3

*Comment*

Acute leukaemias of ambiguous lineage cannot be diagnosed without immunophenotypic information.

**4.2. Myelodysplastic syndromes**

*Definition*

The myelodysplastic syndromes (MDS) are a highly heterogeneous group which usually present with evidence of

bone marrow failure with dysplasia of one or more myeloid cell lineages. The abnormal hematopoietic cells die in great numbers in bone marrow, resulting in cytopenia for one or more myeloid lineages. The myelodysplastic syndromes are the most common precursors of leukaemia.

*Main diagnostic criteria*

- Peripheral blood shows anaemia or cytopenia of at least one myeloid line.
- Bone marrow shows dysplasia, which may be accompanied by increased myeloblasts. Bone marrow aspirate or biopsy are essential for the diagnosis.
- Anomalies should be present in the absence of alcoholism, vitamin deficiency and liver failure.

*Coding rules*

- If refractory anaemia with ringed sideroblasts (RARS) is diagnosed, it is important to check whether another tumour is present. If an associated tumour is present, the associated tumour should be registered and coded and not the RARS. The RARS is considered reactive in this context.
- If myelodysplastic syndrome transforms into acute leukaemia, it is important to check the percentage of blasts in bone marrow:  
<20%: code refractory anaemia with excess blasts 9983/3;  
≥ 20%: code acute myeloid leukaemia (AML).
- If the MDS was diagnosed before the AML, the AML should be registered as transformed.
- If the MDS was not diagnosed before the AML, the AML should be coded as a new incident case.

*Comments*

- If both bone marrow aspirate and biopsy are available for an MDS case, the result of the aspirate takes precedence over the result of the biopsy for coding purposes, except when the aspirate is of poor quality.
- Therapy-related MDS is diagnosed after chemotherapy or radiotherapy.

**Table 4.2.1. - Sub-classification and coding of MDS<sup>7</sup>**

Diagnosis	Blood	Bone marrow		ICD-O-3 code
	Blasts (%)	Blasts (%)	Ringed sideroblasts (%)	
Refractory anaemia <sup>a</sup>	<1	<5	<15	9980/3
Refractory cytopenia with multilineage dysplasia <sup>b</sup>	<1	<5	<15	9985/3
Refractory anaemia with ringed sideroblasts	<1	<5	>15	9982/3
Refractory anaemia with excess of blasts	<5	5-19	Variable	9983/3
5q- chromosome abnormality syndrome	<1	<5	<15	9986/3
MDS, unclassifiable				9989/3

<sup>a</sup>In refractory anaemia, dysplasia is present in one lineage only: the erythroid line.

<sup>b</sup>In refractory cytopenia with multilineage dysplasia, dysplasia is present in at least 10% of the cells of at least two myeloid lines.

- For a case incident in prior to the introduction of ICD-O-3, the case should be coded according to ICD-O-2 to ensure consistency with other data of that incident year.
- Diagnosis of 5q-syndrome (9986/3) requires the results of karyotype analysis.

### 4.3. Chronic myeloproliferative neoplasms

Chronic myeloproliferative neoplasms are characterised by proliferation of one or more myeloid (granulocytic, erythroid or megakaryocytic) lineages in bone marrow, in the presence of normal cellular maturation, resulting in increased numbers of granulocytes, erythrocytes, or platelets in peripheral blood. These cells are morphologically normal, in contrast to the situation in myelodysplastic syndromes.

#### 4.3.1. Chronic myelogenous leukaemia, BCR-ABL positive M-9875/3

##### Definition

Chronic myelogenous leukaemia is a myeloproliferative disease originating in granulocytic lineages and characterised by the presence of a shortened chromosome 22 (Philadelphia chromosome). The Philadelphia chromosome arises as a result of a t(9;22)(q34;q11) translocation and fusion of BCR gene (on chromosome 22) and the ABL gene (on chromosome 9). The BCR/ABL transcript is translated into an aberrant tyrosine kinase.

##### Main diagnostic criteria

- **Bone marrow aspirate/biopsy** shows dysplasia, which may be accompanied by increased myeloblasts and hypercellularity in granulocytic lineage. Bone marrow cytology or bone marrow biopsy are essential for the diagnosis.
- **Peripheral blood** shows neutrophilic leukocytosis, myelemia, persistent thrombocytosis, ± anaemia.
- **Cytogenetics** shows Philadelphia chromosome [t(9;22)].
- **Molecular analysis** reveals BCR-ABL.

##### Coding rules

- For recording incidence date check ENCR rules<sup>1</sup>. Check Table 3.3.2. to determine whether or not a chronic leukaemia has transformed into an acute form.
- The code 9876/3 (atypical chronic myeloid leukaemia, BCR-ABL-negative) implies that the cytogenetic or molecular biology examinations have been performed and found negative. If cytogenetic or molecular biology examinations have not been performed or are not available, the entity is coded as 9863/3 (chronic myeloid leukaemia, NOS).

##### Comment

No other myeloproliferative diseases have the Philadelphia chromosome (are BCR-ABL-positive).

#### 4.3.2. Polycythaemia vera M-9950/3

##### Definition

Polycythaemia vera (PV) is a myeloproliferative disease arising in the erythroid lineage.

##### Main diagnostic criteria

The diagnostic criteria for PV have changed since 2001 and mainly depend on JAK2 mutation status<sup>8</sup>.

1. (a) Haemoglobin >18.5 g/dL in men, >16.5 g/dL in women; or (b) haemoglobin or haematocrit >99th percentile of reference range for age, sex or altitude of residence; or (c) haemoglobin >17 g/dL (men), >15 g/dL (women) if associated with sustained increase in haemoglobin of ≥2 g/dL from baseline and not attributable to correction of iron deficiency or red cell mass >25% above mean predicted normal value.
2. Presence of JAK2V617F or similar mutation.

##### Minor diagnostic criteria

1. Bone marrow biopsy shows hypercellularity with tri-lineage myeloproliferation.
2. Serum erythropoietin below normal.
3. Endogenous erythroid colony *in vitro*.

##### Coding rules

- For recording incidence date check ENCR rules<sup>1</sup>.
- Check Table 3.3.2. to determine whether or not PV has transformed into acute leukaemia.

##### Incidence date

The results of several examinations are necessary for diagnosis of PV; they may be performed over a period of several weeks. The incidence date should be taken as the date on which the histological or cytological sample was taken (priority according to the ENCR rules). If the date on which the sample (usually blood sample) was taken is not available, the date of incidence should be the date of definitive diagnosis.

##### Comment

Polycythemia vera is difficult to diagnose.

#### 4.3.3. Chronic idiopathic myelofibrosis/ Myelosclerosis with myeloid metaplasia M-9961/3

##### Definition

Myelosclerosis with myeloid metaplasia is a clonal myeloproliferative neoplasm characterized mainly by proliferation of megakaryocytes and granulocytes in bone marrow, associated with reactive deposition of fibrous connective tissue in marrow and extramedullary haematopoiesis.



*Main diagnostic criteria*

- **Clinical findings** Splenomegaly.
- **Blood** Hyperleukocytosis, anaemia, variable megakaryocytic proliferation, anisopoikilocytosis (red cells of various size and shape particularly teardrop-shape), myeloma, erythroblastosis.
- **Bone marrow** Fibrosis, hypocellularity.
- **Cytogenetics** No Philadelphia chromosome.
- **Molecular biology** No BCR-ABL fusion gene.

*Comments*

- To determine whether chronic idiopathic myelofibrosis is a transformation of a previously existing HM, check ENCR rules<sup>1</sup> and Table 3.3.2.
- Notwithstanding the presence of splenomegaly, site is bone marrow.
- JAK2 V617F is mutated in 20% to 30% of cases.
- Diagnosis difficult. The clinician should explicitly state the diagnosis before the case is coded as chronic idiopathic myelofibrosis.

**4.3.4. Essential thrombocythaemia M-9962/3***Definition*

Essential thrombocythaemia is a clonal myeloproliferative neoplasm mainly involving the megakaryocytic lineage.

*Main diagnostic criteria*

1. Platelet count  $\geq 450 \times 10^9/L$ .
2. Not meeting WHO criteria for CML, PV, idiopathic myelofibrosis, MDS or other myeloid neoplasm.
3. Demonstration of JAK2V617F or other clonal marker, or no evidence of reactive thrombocytosis.
4. Proliferation of megakaryocytes with large mature morphology. Little or no granulocyte or erythroid proliferation.

*Coding rules*

- To determine whether essential thrombocythaemia is a transformation of a previously existing HM, check ENCR rules<sup>1</sup> and Table 3.3.2.
- Essential thrombocythaemia is difficult to diagnose. The clinician should explicitly state the diagnosis before the case is coded as this entity.
- The diagnostic criteria for essential thrombocythaemia have changed since 2001<sup>8</sup>.

**4.3.5. Chronic neutrophilic leukaemia M-9963/3***Definition*

Chronic neutrophilic leukaemia is a rare myeloproliferative neoplasm, characterised by sustained peripheral blood neutrophilia. Less than 100 cases have been reported in the world. A diagnosis of exclusion.

*Main diagnostic criteria*

- **Blood smear** Peripheral blood leukocytosis  $\geq 25 \times 10^9/L$ .
- **Bone marrow aspirate/biopsy** Hypercellularity with neutrophilic proliferation.
- **Cytogenetics** No Philadelphia chromosome.
- **Molecular biology** No BCR-ABL fusion gene.

**4.3.6. Chronic eosinophilic leukaemia (hypereosinophilic syndrome) M-9964/3***Definition*

Chronic eosinophilic leukaemia/hypereosinophilic syndrome is an uncommon myeloproliferative neoplasm characterized by chronic hypereosinophilia. A diagnosis of exclusion.

*Main diagnostic criteria*

- **Blood** Eosinophilia ( $\geq 1.5 \times 10^9/L$ ).
- **Bone marrow aspirate/biopsy** Hypercellularity due to eosinophilia;  $< 20\%$  blasts in blood or bone marrow.
- **Cytogenetics** Absence of Philadelphia chromosome.
- **Molecular biology** No BCR-ABL fusion gene.
- **Exclusion of other causes of eosinophilia** such as allergies, parasitic disease, infectious disease, collagen vascular disease, lung disease (cancer, hypersensitivity pneumonia), Hodgkin lymphoma, liver cancer, and pancreatic cancer.

**4.3.7. Chronic myeloproliferative disease, NOS M-9960/3***Definition*

Chronic myeloproliferative disease NOS should only be assigned to cases that have definite clinical, laboratory and morphologic features of a myeloproliferative disease, but which fail to meet the criteria for any of the specific CMPN entities, or which present with features that overlap two or more CMPN categories.

*Main diagnostic criteria*

- **Blood smear**  $\pm$  Hyperleucocytosis,  $\pm$  thrombocytosis,  $\pm$  anaemia.
- **Bone marrow aspirate/biopsy** Hypercellularity in bone marrow.
- **Cytogenetics/molecular biology** Absence of the BCR-ABL fusion gene.

*Coding rules*

- To determine whether chronic myeloproliferative disease NOS is a transformation of a previously existing HM, check ENCR rules<sup>1</sup> and Table 3.3.2.
- When there is suspicion of chronic myeloid leukaemia, or molecular biology examinations are negative, the case should be classified as 9876/3 (atypical chronic leukaemia, BCR-ABL negative).

#### 4.4. Myelodysplastic/myeloproliferative neoplasms

##### Definition

The category myelodysplastic/myeloproliferative neoplasms was created by the authors of the WHO manual of 2008 because some neoplasms have characteristics of both myeloproliferative neoplasms and myelodysplastic syndrome<sup>5</sup>.

##### Coding rules

The category myelodysplastic/myeloproliferative neoplasms is recognized in the WHO classification<sup>5</sup>, but is not present in ICD-O-3; it includes the following entities: chronic myelomonocytic leukaemia (ICD-O-3 code 9945/3); juvenile chronic myelomonocytic leukaemia (ICD-O-3 code 9946/3); atypical chronic myeloid leukaemia (BCR-ABL negative) (ICD-O-3 code 9876/3); and MDS/MPN unclassifiable (ICD-O-3 code 9975/3).

##### 4.4.1. Chronic myelomonocytic leukaemia **M-9945/3**

##### Definition

Chronic myelomonocytic leukaemia (CMML) is a dysplastic myeloproliferative disease of granulocytic and monocytic lineages.

##### Main diagnostic criteria

- **Peripheral blood** Blasts: <5% together with monocytes:  $>1 \times 10^9/L$ .
- **Bone marrow** Blasts: <20%, together with ring sideroblasts (variable percentage).
- **Cytogenetics** No Philadelphia chromosome.
- **Molecular biology** No BCR-ABL fusion gene.
- **All other causes of monocytosis excluded.**

##### Comment

Bone marrow smear/biopsy mandatory.

##### 4.4.2. Juvenile myelomonocytic leukaemia **9946/3**

##### Definition

Juvenile myelomonocytic leukaemia (JMML) is a dysplastic myeloproliferative disease of granulocytic and monocytic lineages occurring in children of age <14 years.

##### Main diagnostic criteria

At least two or the following:

- Foetal haemoglobin high for age
- Immature granulocytes in peripheral blood
- White blood cell count  $>10 \times 10^9/L$
- Clonal chromosomal abnormality (e.g., monosomy 7)

- Myeloid progenitors hypersensitive to GM-CSF *in vitro*

##### Coding rules

- To determine whether JMML is a transformation of a previously existing HM, check ENCR rules<sup>1</sup> and Table 3.3.2.

##### 4.4.3. Atypical chronic myeloid leukaemia BCR-ABL negative **M-9876/3**

##### Definition

Atypical chronic myeloid leukaemia is a chronic myeloproliferative neoplasm mainly involving the neutrophil series, without the Philadelphia chromosome or BCR-ABL fusion gene.

##### Main diagnostic criteria

- High neutrophil count, immature granulocytes, thrombocytosis,  $\pm$  anaemia.
- Absence of Philadelphia chromosome.
- Absence of BCR-ABL fusion gene.
- Hypercellularity in bone marrow.

##### Coding rules

- To determine whether atypical chronic myeloid leukaemia is a transformation of a previously existing HM, check ENCR rules<sup>1</sup> and Table 3.3.2.
- The M-9876/3 code can only be used when cytogenetic or molecular analyses have been found negative.
- When neither cytogenetic nor molecular analysis have been performed, use code 9863/3 (chronic myeloid leukaemia, NOS).

##### 4.4.4. Myelodysplastic/myeloproliferative neoplasm, unclassifiable **M-9975/3**

##### Main diagnostic criteria (WHO<sup>5</sup>)

Presence of clinical, laboratory and morphologic features of one of the categories of MDS, with <20% blasts in bone marrow

**And** prominent myeloproliferative features:

- Platelet count  $\geq 600 \times 10^9/L$  with megakaryocytic proliferation **Or**
- White blood cell count  $\geq 13 \times 10^9/L$  with or without prominent splenomegaly

**And** no previous history of underlying CMPN or MDS, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic or myeloproliferative features, and no Philadelphia chromosome, del(5q), t(3;3)(q21;q26) or inv(3)(q21;26)

**Or** the patient has mixed myeloproliferative and myelodysplastic features and cannot be assigned to any another category of MDS, CMPN or MDS/MPN.

## 5. Lymphoid malignancies

### 5.1. Definition and classification

The WHO classification of 2008<sup>5</sup> recognises three major categories of lymphoid neoplasms: B cell neoplasms, T and NK cell neoplasms, and Hodgkin lymphoma. The distinction between Hodgkin lymphoma and non-Hodgkin lymphoma has been obsolete for some time and the old “non-Hodgkin” lymphoma category is now recognised have included a large number of distinct entities each with distinctive epidemiology, aetiology and clinical features, and sometimes differing response to therapy. Both lymphomas and lymphoid leukaemias are lymphoid malignancies, since both solid and circulating phases are present in many lymphoid neoplasms. Thus, B-cell chronic lymphocytic leukaemia and B-cell small lymphocytic lymphoma are considered the same neoplasm, but have differing clinical presentation.

The WHO classification of lymphoid malignancies<sup>5,9</sup> was based on that of the Revised European-American Classification of Lymphoid Neoplasms (REAL) which adopted the principle of using all available information – morphology, immunophenotype, genetic features and clinical features – to define a disease entity<sup>10</sup>. Although while the relative importance of these features varies between entities, morphology is always important. Many diseases are primarily defined by morphology, with immunophenotype as backup. Some diseases have a virtually specific immunophenotype, so that the diagnosis is unlikely in the absence of the immunophenotype. Some lymphomas are characterized by a specific genetic abnormality. Still others require knowledge of clinical features as well as nodal vs. extranodal presentation, or specific anatomic site. Nevertheless classification is often complicated by the biological and clinical polymorphism displayed by many of these diseases.

**Table 5.1.1. - Immunophenotypic classification of lymphoid malignancies<sup>7</sup>**

Marker	Cell type	Disease
CD3	T-lymphocyte	T- lymphoid haemopathy
CD4	T-lymphocyte with cytokine secretion	T- lymphoid haemopathy
CD5	Normal T-lymphocyte and B-lymphocyte in CLL/SLL	CLL/SLL Mantle cell lymphoma
CD7	T-lymphocyte	T- lymphoid haemopathy
CD8	Cytotoxic T-lymphocyte	T- lymphoid haemopathy NK and T-cytotoxic lymphoid haemopathies
CD10	Pre-B lymphoblast Follicular lymphocyte	pre-B ALL Follicular lymphoma
CD16	Granulocyte, macrophage, NK lymphocyte	NK lymphoid haemopathies
CD19	B-lymphocyte	B-lymphoid haemopathy
CD20	B-lymphocyte	B-lymphoid haemopathy
CD23	B-lymphocyte	B-CLL
CD30 (Ki-1, obs)	Activated lymphocyte (not found in normal lymphocyte)	Hodgkin lymphoma Anaplastic lymphoma Cutaneous lymphomas
CD45	Haemopoietic cell (except erythroblasts)	Haemopoietic neoplasms
CD56	NK lymphocyte	NK lymphoid haemopathies
ALK (anaplastic lymphoma kinase)	Marker of t(2;5) translocation involving ALK gene.	Large cell anaplastic lymphoma
Bcl 2	Inhibitor of apoptosis	Follicular lymphomas
Ki-67	Cycling cell (not in G0)	Mantle cell lymphoma
Cyclin D1	Cycling cell	Mantle cell lymphoma
The cytotoxicity markers: Perforin Granzyme B T-antigen	Cytotoxic T-lymphocytes NK lymphocytes	NK and T-cytotoxic Lymphoid haemopathy

## 5.2. Registration rules for lymphoma topography

It is usually impossible to determine the primary site when multiple sites are involved. Visceral or marrow sites cannot be registered unless there is microscopic confirmation from biopsies or smears of these sites.

- When both visceral and lymph node localizations are present, code the visceral site.
- When both marrow and lymph node localizations are present, code marrow.
- When a single visceral site and bone marrow are involved, with or without nodal localization:
  - a. with histological diagnosis of visceral involvement, code the visceral site;
  - b. without histological diagnosis of visceral involvement, code marrow.

Examples:

- biopsies show gastric involvement and bone marrow involvement: code stomach (C16\_);
- imaging diagnoses lung involvement without biopsy, but bone marrow involvement evident on smear/biopsy: code marrow (C42.1).
- When multivisceral and marrow localizations are present, with or without lymph node involvement, code marrow (C42.1).
- When multivisceral localizations are present, without marrow involvement, code C77.8 (lymph nodes of multiple regions) must be used (there is no multivisceral topography code).
- When a single mediastinal mass is present, code mediastinum (C38.\_).
- Splenectomy is required to demonstrate spleen involvement. Remember that spleen is considered a lymphatic tissue not a visceral tissue.
- When a single nodal site is involved, code C77.\_.
- When lymph nodes of multiple regions are involved, code C77.8.

## 5.3. Lymph node topography

Lymph node topography is coded according to ICD-O-3. Many lymphatic tissues have specific codes, for example spleen (C42.2), Waldeyer ring (C14.2) and tonsil (C09.\_). Mediastinal lymphomas lacking more precise location data should be coded C38.3 (mediastinum). Codes C77.0 to C77.5 (Table 5.3.1.) are reserved for body regions whose lymphatic tissues do not have more specific codes.

**Table 5.3.1. - ICD-O-3 codes for lymph node sites without more specific topography codes<sup>4,7</sup>**

Lymph node topography	Comment	ICD-O-3 topography
Head, face and neck		C77.0
Intrathoracic		C77.1
Intra-abdominal		C77.2
Axilla or arm		C77.3
Inguinal region or leg		C77.4
Pelvic		C77.5
Multiple regions	Two or more regions	C77.8
Lymph node, NOS	Lymph node origin	C77.9

## 5.4. Registration rules for transformations of non-Hodgkin lymphomas

1. Transformation of small cell non-Hodgkin lymphoma into large cell non-Hodgkin lymphoma
  - a. When a small cell non-Hodgkin lymphoma transforms into a large cell non-Hodgkin lymphoma, irrespective of the date of transformation (and even if the two entities were diagnosed at the same time) the small cell lymphoma must always be the one that is registered. The subsequent large cell transformation can be recorded in a separate archive as a daughter tumour (specifying the date on which it evolved from the previous entity, its topography and its morphology).
  - b. A transformed large cell non-Hodgkin lymphoma is never an incident disease and must not be included in incidence data, according to ENCR and ICD-O-3 rules.
2. An *undetermined* lymphoma should preferably be coded M-9591/3 (malignant lymphoma, non-Hodgkin, NOS) rather than M-9590/3 (which can include Hodgkin disease). The M-9590/3 code should be used if the pathologic report explicitly mentions uncertainty as to whether the disease is non-Hodgkin or Hodgkin lymphoma.
3. Immunoproliferative diseases with behaviour code /3 must be registered as one of the following:
  - Immunoproliferative disease, NOS, M-9760/3
  - Waldenström macroglobulinaemia (C42.0), M-9761/3
  - Heavy chain disease, NOS, M-9762/3
  - Immunoproliferative small intestinal disease (C17.\_), M-9764/3
4. Immunoproliferative diseases with behaviour code /1 must not be registered, these include:
  - Angiocentric immunoproliferative lesion (lymphoid granulomatosis), M-9766/1
  - T-gamma lymphoproliferative disease, M-9768/1
  - Immunoglobulin deposition disease, M-9769/1
  - Monoclonal gammopathy, NOS, M-9765/1

Note that angioimmunoblastic lymphadenopathy (M-9767/1) is now considered a T-lymphoma. If encountered it must be coded as M-9705/3 (angioimmunoblastic T-cell lymphoma)

5. T-cell large granular lymphocytic leukaemia (T-LGL, M-9831/1) must be registered. Although the ICD-O-3 gives it with behaviour code /1, it is considered malignant /3 by the WHO.
6. Although cutaneous follicle centre malignant lymphomas are an established category, they are not mentioned in ICD-O-3 classification. They must be coded as M-9690/3 (follicular lymphoma, NOS) with topography code C.44.\_.
7. Castleman's disease must not be registered.

**5.5. Staging of lymphoid malignancies**

Lymphoid malignancies are not like other solid tumours (that have a primary site and secondary metastatic sites). A TNM staging system is therefore inappropriate for lymphomas and the term *metastasis* is not used. The extent of most lymphomas is specified by the four-stage Ann Arbor staging system (Table 5.5.1.) based on disease localization(s) at time of diagnosis. A separate staging system has been developed for multiple myelomas.

**5.6. Precursor B- and T-cell neoplasms**

**5.6.1. Precursor B-cell lymphoblastic leukaemia/lymphoma** **M-9836/3, M-9728/3**

*Definition*

Precursor B-cell lymphoblastic leukaemia/lymphoma is a neoplasm of lymphoblasts committed to the B-cell

lineage. The entity B-ALL (precursor B-cell lymphoblastic leukaemia, acute lymphoblastic leukaemia, M-9836/3) should be registered when the disease presents with bone marrow and peripheral blood involvement. Precursor B-lymphoblastic lymphoma (M-9728/3) should be entered when an extra medullary mass lesion is found together with ≤25% lymphoblasts in bone marrow.

*Immunophenotype*

CD19+, cytoplasmic CD79a+, CD10+/-, CD24+/-, TdT+, CD20-/+ , CD22+/-, CD45+/-, cytoplasmic and surface-Ig-(/+) depending on the degree of differentiation and on cytogenetic alterations.

**5.6.2. Precursor T-cell lymphoblastic leukaemia/lymphoma** **M-9837/3, M-9729/3**

*Definition*

Precursor T-cell lymphoblastic leukaemia/lymphoma is a neoplasm of lymphoblasts committed to the T-cell lineage, it involves bone marrow and peripheral blood, or nodal or extranodal tissues.

*Immunophenotype*

TdT+, cytoplasmic or surface CD3+ and CD7+, co-expression of CD4 and CD8, CD1a+/-, CD2+/-, CD4+/-, CD5+/-, CD8+/-, CD10-/+ , CD79a-/+.

*Main diagnostic criteria*

1. Presence of lymphoblasts in lymph node or tissue biopsy
  - a. Marrow aspirate/biopsy shows <20% lymphoblasts: lymphoblastic lymphoma.

**Table 5.5.1. - Ann Arbor staging system classification for lymphomas (Cotswolds revision)<sup>11,12</sup>**

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, or Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (mediastinum is a single site; hilar lymph nodes are lateralized); the number of anatomic sites should be indicated by suffix (e.g., II <sub>3</sub> )
III	Involvement of lymph node regions or structures on both sides of the diaphragm
III <sub>1</sub>	With or without splenic, hilar, celiac or portal hepatic nodes
III <sub>2</sub>	With para aortic, iliac or mesenteric nodes
IV	Involvement of extranodal site(s) beyond these designated E (extranodal)
<b>Annotations</b>	
A	No symptoms
B	Fever, drenching sweats or weight loss
X	Bulky disease: >1/3 width of mediastinum at T5-6, or >10 cm
E	Involvement of a single extranodal site contiguous with or proximal to the known nodal site of disease
CS	Clinical stage
PS	Pathologic stage



- b. Marrow aspirate/biopsy shows >20% lymphoblasts: acute lymphoblastic leukaemia.

#### Coding rules

1. If immunophenotyping cannot distinguish between B- and T-cell disease, the code M-9727/3 (lymphoblastic lymphoma, NOS) should be used.
2. The WHO classification and the ICD-O-3 no longer distinguish between *lymphoblastic lymphoma* and *acute lymphoblastic leukaemia*<sup>4,5</sup>. Although the ICD-O-3 has two codes (M-9837/3 and M-9729/3) it asks that for analysis purposes the two entities be considered together. However to make it possible to perform comparative analyses with previous studies that considered these entities separately, cancer registries are asked to maintain the coding distinctions:
  - Lymphoblastic lymphoma (9729/3):
    - mainly nodal involvement
    - marrow blasts <20%
  - Acute lymphoblastic leukaemia (9837/3):
    - mainly bone marrow involvement
    - marrow blasts ≥20%.

### 5.7. Mature B-cell neoplasms

Mature B-cell neoplasms include non-Hodgkin B-cell malignant lymphomas and chronic lymphoproliferative disease of B-cell origin. About 85% of non-Hodgkin lymphomas are in fact mature B-cell neoplasms, and about half of mature B-cell neoplasms consist of large B-cell and follicular types.

#### 5.7.1. Chronic lymphocytic leukaemia/small lymphocytic lymphoma M-9823/3, M9670/3

##### Definition

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) are neoplasms of small lymphocytes mixed with prolymphocytes and para-immunoblasts. When they present in peripheral blood or bone marrow they are coded as M-9823/3 (CLL). Non-leukaemic cases with possible lymph node or extranodal dissemination are coded as M-9670/3 (SLL).

##### Immunophenotype

s-IgM+/-, s-IgD+/-, CD19+, CD5+, CD23+, CD43+, CD11c+, FMC7-/+ , CD79b-/+.

##### Main diagnostic criteria

- Chronic lymphatic leukaemia (CLL)
  - blood count shows lymphocytes >4 x 10<sup>9</sup>/L
- Small lymphocytic lymphoma (SLL)
  - blood count shows lymphocytes ≤4 x 10<sup>9</sup>/L
  - lymph node biopsy shows proliferation of neoplastic small “mature” B-lymphocytes

#### Coding rules

1. As noted above, transformations into large cell forms should be recorded in a separate archive entry as a daughter tumour (with date of transformation, topography and morphology).
2. The WHO classification<sup>5</sup>, and ICD-O-3<sup>4</sup> no longer distinguish between CLL and SLL, although they do present with differing clinical features: CLL is characterized by mainly marrow and peripheral blood involvement (circulating lymphocytes >4 x 10<sup>9</sup>/L). SLL mainly involves lymph nodes or tissue (circulating lymphocytes ≤4 x 10<sup>9</sup>/L). ICD-O-3 retains separate codes for these entities; and to make it possible to perform comparative analyses with previous studies, cancer registries are asked to retain them. However it is recommended that future analyses should consider these entities as one<sup>4</sup>.
3. A CLL diagnosis cannot be based on blood count only. An immunophenotypic investigation (preferably) or marrow examination is required. In the absence of both the latter test results, the specialist’s assessment can be used, but to maintain high quality cancer registration, codings based on specialist’s opinion without test results should be few in number.
4. Of all dates available, the incidence date for a CLL must be that which occurs highest in the following list:
  - a. date of immunophenotypic assessment
  - b. date of marrow aspiration/biopsy
  - c. date of blood count ordered by specialist who made diagnosis
  - d. date of specialist’s diagnosis.
 If several blood count dates are available (but not immunophenotypic assessment or marrow examination), the incidence date will be the date of blood examination ordered by the specialist who made diagnosis. In high-quality cancer registries, incidence dates are rarely assigned in this fashion.
5. The Ann Arbor staging system is used only for SLL, not for CLL.

#### 5.7.2. Prolymphocytic leukaemia B-cell type M-9833/3

##### Definition

Prolymphocytic leukaemia B-cell type (B-PLL) is a neoplasm of prolymphocytes of B-cell lineage that presents in blood (with prolymphocyte count exceeding 55% of all lymphocytes), bone marrow and spleen.

CLL with prolymphocytic transformation and CLL with increased prolymphocytes (CLL/PL) are excluded from B-PLL.

##### Immunophenotype

s-IgM+, s-IgD+/-, CD79b+, FMC7+, CD5+ in 1/3 of cases, CD19+, CD20+, CD23-.

*Main diagnostic criteria*

Blood count shows prolymphocytes (large atypical cells with large nucleolus) constituting >55% (usually over 100,000/mm<sup>3</sup>) of total lymphocytic count.

*Coding rules*

B-cell pro-lymphocytic leukaemia does not transform.

**5.7.3. Lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia M-9671/3, M-9761/3**

*Definition*

Lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia (LPL/WM) are clonal neoplastic proliferations of small B lymphocytes, plasmacytoid lymphocytes and plasma cells. Bone marrow, lymph nodes and spleen are the most frequent sites. Most cases are associated with the presence of an IgM-type monoclonal serum protein that results in blood hyper-viscosity and cryoglobulinaemia (Waldenström macroglobulinaemia).

There is a gamma heavy chain variant of this condition whose characteristic feature is secretion of a truncated gamma chain lacking light chain binding sites (ICD-O code M-9762/3).

*Immunophenotype*

s-Ig+ (usually IgM, sometimes G, rarely A), c-Ig+ (in subpopulation of cells), IgD-, CD5-, CD10-, CD23-, CD43+/-, CD38+.

*Main diagnostic criteria*

1. Bone marrow aspirate or biopsy: infiltration of lymphoplasmacytic polymorphic cells (lymphocytes, plasma cells and intermediate cells).
2. When a pathological report is available specifying lymphoplasmacytic lymphoma, code M-9671/3, otherwise code M-9761/3 (Waldenström macroglobulinaemia, C.42.0).

*Coding rules*

1. LPL and WM are prone to transformation.
2. The WHO and ICD-O-3 classifications no longer distinguish between LPL and WM. However ICD-O-3 retains separate codes for LPL (9671/3) and WM (9761/3)<sup>4,5</sup>. The recommendation is that these entities be treated together in future analyses, but that separate codes be retained to make it possible to perform comparative analyses compatible with past data. The separation is based on protein examination:
  - monoclonal IgM peak: code WM (M-9761/3);
  - absence of monoclonal IgM peak: code LPL (M-9671/3).

According to Bladé LPL/WM are no longer distinguished on the basis of IgM peak, but on preponderance of nodal involvement<sup>3</sup>.

**5.7.4. Splenic marginal zone lymphoma M-9689/3**

*Definition*

Splenic marginal zone lymphoma is a neoplasm of small lymphocytes and transformed blasts originating in the marginal zone of splenic white pulp, with dissemination into the red pulp. The presentation is frequently leukaemic but bone marrow and splenic hilar lymph nodes are also involved. Leukaemic cells may have a villous-lymphocyte morphology.

*Immunophenotype*

s-IgM+, s-IgD+, C19+, CD5-, CD23-, CD10-, CD43-, CD103-, cyclin D1-.

*Main diagnostic criteria*

Spleen biopsy shows proliferation of neoplastic B-lymphocytes in the marginal zone of the follicle.

*Coding rules*

1. Splenic marginal zone lymphoma can turn into large B-cell lymphoma.
2. If immunologic markers are not concordant with biopsy evidence, the biopsy result takes precedence for coding purposes.
3. When villous lymphocytes in circulating blood and splenomegaly are present, the splenic origin of the lymphoma can be accepted without histological confirmation (spleen is not biopsied). The topographic code C42.2 is automatically associated with splenic marginal zone lymphoma (M-9689/3).

**5.7.5. Hairy cell leukaemia M-9940/3**

*Definition*

Hairy cell leukaemia is a neoplasm of small B-cells of characteristic morphology comprising oval nuclei, abundant light cytoplasm, and 'hairy' projections on plasma membrane. The disease involves peripheral blood, bone marrow and splenic red pulp.

*Immunophenotype*

s-Ig+ (M+/-D, G or A), CD79b-, CD5-, CD10-, CD23-, CD11c+, CD25+, FMC7+, CD103+, tartrate-resistant acid phosphatase+, DBA.44+, annexin+.

*Main diagnostic criteria*

1. Blood count shows pancytopenia of variable severity.
2. Blood sample or marrow aspirate/biopsy shows presence of small B-lymphoid cells with hairy projections. Marrow biopsy shows fibrosis.

*Coding rules*

Hairy cell leukaemia does not transform.

**5.7.6. Plasma cell neoplasms**

These neoplasms result from the expansion of a clone of immunoglobulin (Ig) secreting, heavy chain switched, terminally differentiated B cells secreting a monoclonal immunoglobulin called *paraprotein* or *M-protein*. The presence of such a protein is known as monoclonal gammopathy. The true plasma cell neoplasms discussed here are plasma cell myeloma (with the monoclonal gammopathy of uncertain significance as a precursor lesion) and plasmacytoma.

**Multiple myeloma****M-9732/3***Definition*

Plasma cell myeloma is multifocal neoplasm based in bone marrow. It is characterized by a monoclonal protein in serum and osteolytic lesions with bone fractures, pain, hypocalcemia and anaemia. Pathological, radiological and clinical data are required to secure the diagnosis.

*Variants:* non-secretory myeloma, indolent myeloma, smoldering myeloma, plasma cell leukaemia.

*Immunophenotype*

CD19-, CD20-/+, CD38+, CD138+, CD79a+, CD56+/-, monotypic cytoplasmic immunoglobulins (usually IgG).

*Main diagnostic criteria*

See WHO manual of 2008<sup>5</sup>.

1. *Symptomatic plasma cell myeloma*

- M-protein in serum or urine (in most cases M-protein is >30 g/L of IgG or >25 g/L of IgA or 1 g/24h of urine light chain, but some patients have levels lower than these).
- Bone marrow clonal plasma cells or plasmacytoma (no minimal level is designated: monoclonal plasma cells usually exceeds 10% of nucleated cells in the marrow, but about 5% of patients have levels lower than these).
- Related organ or tissue impairment (*CRAB*: hypercalcaemia, renal insufficiency, anaemia, bone lesions).

*The most important criteria for symptomatic myeloma are manifestations of end organ damage including anaemia, hypercalcaemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis or recurrent infections.*

2. *Asymptomatic (smoldering) myeloma*

- M-protein in serum at myeloma levels (>30 g/L)  
**And/Or**

- 10% or more clonal plasma cells in bone marrow
- No related organ or tissue impairment (end organ damage or bone lesions [*CRAB*] or myeloma related symptoms).

**Monoclonal gammopathy of undetermined significance (MGUS) M-9765/1***Definition*

MGUS reflects the presence of an expanded clone of immunoglobulin-secreting cells. This process is not considered neoplastic since it does not always progress to malignancy. It may precede the development of an overt myeloma.

MGUS may occur in IgM and non-IgM forms. They have identical clinical presentation, but different genetic bases and different outcomes in terms of malignant progression.

The presence of a small IgM paraprotein (IgM MGUS) is associated with a lymphoplasmacytic clone that may progress to a lymphoplasmacytic lymphoma and/or Waldenström macroglobulinemia (WM). Non-IgM MGUS (IgG, IgA) is associated with clonal plasma cells and it may progress to a malignant plasma cell neoplasm.

*Immunophenotype*

CD19-, CD56+/-, CD 38+ (weak).

*Main diagnostic criteria<sup>5</sup>*

- M-protein in serum <30g/L
- Bone marrow clonal plasma cell <10% and low level of plasma cell infiltration in a trephine biopsy
- No lytic bone lesions
- No myeloma-related organ or tissue impairment (*CRAB*)
- No evidence of other B-cell proliferative disorder

*Coding rules*

According to the ENCR rules<sup>1</sup> plasma cell myeloma can be registered without bone marrow aspirate/biopsy when the monoclonal component is >35 g/L for IgG and >20 g/L for IgA.

1. A clinician's explicit diagnosis of myeloma is important when immunoglobulin levels are below the threshold and when a marrow aspirate/biopsy is not available. The protein immunoelectrophoresis (or immunofixation) results and hospital discharge diagnosis should be archived for later checking.
2. Difficult or problematic cases are common in view of the inherent difficulty in distinguishing myeloma from smoldering myeloma, so again an explicit diagnosis is important. In some cases it may be useful to consult a haematologist for advice.



3. Marrow biopsy can reveal clusters of neoplastic plasma cells undetected by aspirate, so the marrow biopsy result takes precedence.
4. Plasma cell myeloma can transform into plasma cell leukaemia and in this case is coded as a transformation.
5. Non-secretory myeloma is a rare form without immunoglobulin peak.

*Staging criteria for myelomas*

Myelomas are not staged by the Ann Arbor system. Instead the International Staging System of the International Myeloma Working Group is used<sup>13</sup>.

**Table 5.7.6.1. - International Staging System for myeloma**

Stage	Criteria
I	$\beta_2$ microglobulin <3.5mg/L + albumin $\geq$ 3.5g/dL
II	$\beta_2$ microglobulin <3.5mg/L + albumin <3.5g/dL <b>Or</b> $\beta_2$ microglobulin between 3.5 and 5.5 mg/L
III	$\beta_2$ microglobulin >5.5 mg/L

**Solitary plasmacytoma of bone; extra osseous plasmacytoma**

**M-9731/3; M-9734/3**

*Main diagnostic criteria*

1. Lesion biopsy shows proliferation of plasma cells
2. Bone marrow aspirate normal
3. Protein electrophoresis may or may not show an immunoglobulin peak

*Coding rules*

1. According to ICD-O-3, plasmacytoma, NOS necessarily has an osseous topography (C40.\_ or C41).
2. ICD-O-3 code M-9734/3 refers to extra medullary plasmacytoma. According to the WHO classification (2008) this entity is extra osseous plasmacytoma.
3. Plasmacytoma can transform to myeloma, in such cases the myeloma is not considered as incident.
4. Bone marrow aspirate shows normal myeloid cell count.

**5.7.7. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) M-9699/3**

*Definition*

MALT lymphoma is an extranodal neoplasm composed of morphologically heterogeneous small B-cells, centrocytoid cells and monocytoid cells, together with scattered centroblasts and immunoblasts; there may also be a clonal plasma cell component in some cases. The neoplasm may infiltrate epithelial tissues forming lymphoepithelial lesions.

MALT lymphoma is often associated with microbial or autoimmune inflammation (*Helicobacter pylori* gastritis, Sjögren syndrome, Hashimoto thyroiditis).

*Sub-types:* immunoproliferative small intestinal disease (IPSID, ICD-O-3 M-9764/3), alpha heavy chain disease (ICD-O-3 M-9762/3).

*Immunophenotype*

IgM+/-, IgA-/, IgG-/+ with light chain restriction, CD5-, CD10-, CD23-, CD43+/-, CD11c+/, C19+, CD20+, cyclin D1- (thus, no specific immunophenotypic features used to exclude other conditions).

*Sub-types:* immunoproliferative small intestinal disease (IPSID, ICD-O-3 M-9764/3); alpha heavy chain disease (ICD-O-3 M-9762/3).

*Main diagnostic criteria*

Lymph node or tissue biopsy shows proliferation of B lymphocytes of marginal zone of the lymphocytic follicle.

*Coding rules*

1. MALT lymphoma may transform into non-Hodgkin large cell lymphoma.
2. If immunophenotype and biopsy findings are in conflict, the biopsy takes precedence for coding purposes.
3. When villous lymphocytes in circulating blood are coupled with splenomegaly, the splenic origin of the lymphoma can be accepted without histological confirmation (spleen is not biopsied).

**5.7.8. Marginal zone B-cell lymphoma, NOS**

**M-9699/3**

*Definition*

Nodal marginal zone B-cell lymphoma is a primary nodal lymphoma that morphologically resembles marginal zone lymphoma of extranodal type or splenic type; it often has a prominent monocytoid B-cell component.

*Immunophenotype*

IgM+/-, IgA-/, IgG-/+ with light chain restriction. CD5-, CD10-, CD23-, CD43+/-, CD11c+/- (thus, no specific immunophenotypic features used to exclude other conditions). In some cases IgD is positive and CD43 is negative – like splenic marginal zone lymphoma.

**5.7.9. Follicular lymphoma, NOS**

**M-9690/3**

*Definition*

Follicular lymphoma is a neoplasm of germinal centre B cells (centrocytes and centroblasts) of the lymphoid follicle, that exhibits at least a partial follicular growth pattern. Most cases have the t(14;18) chromosomal translocation resulting in non-physiological expression of the Bcl-2 protein. The neoplasm is graded according to the proportion

of centroblasts (large non-cleaved follicular centre cells with basophilic cytoplasm) as determined by high power field microscopy (0.159 mm<sup>2</sup> field, 40x objective).

#### Immunophenotype

Usually surface Ig+ (with heavy chain type of IgM +/-, IgD, IgG, or rarely IgA), CD10+, CD23+/-, Bcl-2+/-, Bcl-6+, CD5-, CD43- (occasional grade 3 cases show CD43+).

#### Main diagnostic criteria

Lymph node or tissue biopsy shows proliferation of lymphocytes of follicular centre origin.

**Table 5.7.9.1. Grades and codes for follicular lymphoma**

Grade	Lymph node or tissue biopsy	ICD-O-3 code
1	0-5 centroblasts per high power field	M-9695/3
2	6-15 centroblasts per high power field	M-9691/3
3	>15 centroblasts per high power field	M-9698/3
3A	Centrocytes present	M-9698/3
3B	Solid sheets of centroblasts	M-9698/3

#### Coding rules

1. Follicular lymphoma can transform into large cell lymphoma.
2. The entity *malignant lymphoma, mixed small and large cell, diffuse* (M-9675/3) is considered obsolete. The ICD-O-3 recommends recoding this as follicular lymphoma NOS (M-9690/3)<sup>4</sup>. This is incorrect from a pathological point of view and is contrary to the WHO classification<sup>5</sup> which considers *malignant lymphoma, mixed small and large cell, diffuse* as *malignant lymphoma, large B-cell, diffuse, NOS* (M-9680/3).

If a small and large cell and diffuse lymphoma is also described as *follicular* it should be coded as follicular lymphoma (M-9690/3) as even if there is a large proportion of large cells.

#### 5.7.10. Mantle cell lymphoma M-9673/3

##### Definition

Mantle cell lymphoma is a B-cell lymphoma originating from the mantle zone of the lymphoid follicle. It consists of monomorphous small-to-medium sized lymphocytes whose nuclei have irregular contours (centrocytoid-like nuclei). The disease is characterised by the t(11;14) chromosome translocation resulting in overexpression of the cell cycle-regulating protein, cyclin D1.

Variants include the blastoid variant with cells resembling lymphoblasts and a high mitotic rate.

##### Immunophenotype

s-IgM +/-, s-IgD, CD5+(/-), cyclin D1+, CD23-, CD43+, FMC7+, Bcl-6-, CD10-

#### Main diagnostic criteria

Lymph node or tissue biopsy is required.

#### Coding rules

1. Mantle cell lymphoma can transform into large cell lymphoma.
2. Do not confuse *nodular* (usually signifying nodular shape) with *follicular* (originating from a follicular centre). A mantle cell lymphoma can have a nodular architecture, but it would not be a follicular (germinal centre) lymphoma.
3. Mantle cell lymphoma may have a leukaemic (blastic) phase; however it must be coded as a lymphoma.

#### 5.7.11. Diffuse large B-cell lymphoma, NOS M-9680/3

##### Definition

A diffuse neoplastic proliferation of large (about twice normal size) B lymphocytes with basophilic cytoplasm and open chromatin, and a variable range of other cytological features. Centroblastic and immunoblastic morphologies are the most common. Most cases have transcriptional resemblance either to germinal centre centroblasts (also known as germinal centre B-cells) characterized by ongoing somatic hyper mutations and antigen class switching, or to post germinal centre phase lymphocytes (with activated B-cell signature).

##### Immunophenotype

Ig+/- (IgM >IgG >IgA), c-Ig-/+ , CD10+/-, Bcl-6+/-, MUM-1/IRF4+/-, Bcl-2+/-, CD5-/+ , CD30-/+

*Variants:* centroblastic, immunoblastic, T-cell/histiocyte rich, anaplastic (unrelated to anaplastic large cell lymphoma of cytotoxic T-cell origin), and plasmablastic [often associated with HIV infection or other altered immune status, with oral cavity being a common site; CD20-(/+), CD45-(/+), CD38+, CD138+].

#### Main diagnostic criteria

Lymph node or tissue biopsy shows proliferation of large B lymphocytes (centroblasts) with diffuse growth pattern.

#### Coding rules

1. A malignant lymphoma small and large cells diffuse (M-9675/3 according to ICD-O-3, but now considered obsolete) should be coded as malignant lymphoma, large B-cell, diffuse, NOS (M-9680/3).
2. A small and large cell and diffuse lymphoma also described as *follicular* should be coded as *follicular lymphoma NOS* (M-9690/3).
3. The ICD-O-3 classification distinguishes *immunoblastic lymphoma* (M-9684/3) from *diffuse large B-cell lymphoma* (M-9680/3). However WHO 2008 classification considers the former to be a vari-

ant of the latter. Thus it is recommended that only the code M-9680/3 be used.

4. According to the ICD-O-3, the category *malignant lymphoma, large B-cell diffuse* (M-9680/3) includes:
  - a. Intravascular lymphoma: large B-cell lymphoma arising from small blood vessel walls.
  - b. T-cell rich, large B-cell lymphoma: large B-cell lymphoma with prominent reactive T-cell component.
  - c. Anaplastic large B-cell lymphoma: anaplastic T or null large cell lymphoma with a separate ICD-O-3 code.

#### 5.7.12. Mediastinal (thymic) large B-cell lymphoma M-9679/3

##### Definition

Mediastinal large B-cell lymphoma is a subtype of diffuse large B-cell lymphoma thought to originate from thymic B-cells. This entity may have morphologic, immunophenotypic and transcriptional characteristics that suggest classic Hodgkin lymphoma.

##### Immunophenotype

CD19+, CD20+, CD30+/-, CD10-, CD5-, CD45+, s-Ig+/-

##### Main diagnostic criteria

Mediastinal biopsy shows a proliferation of large B-cells associated with variable fibrosis.

##### Coding rules

1. Like all large cell lymphomas, mediastinal large B-cell lymphoma does not transform.
2. Large cell mediastinal lymphoma is a distinct entity defined by mediastinal localisation supported by epidemiological (mainly in women between 30 and 50 years), clinical (mediastinal mass symptoms) and pathological (associated sclerosis) features. It is distinct from other non-Hodgkin lymphomas that may have a mediastinal location.

#### 5.7.13. Intravascular large B-cell lymphoma M-9680/3

##### Definition

A rare subtype of diffuse large B-cell lymphoma with presentation restricted to the intravascular space mainly of small blood vessels and capillaries. Common sites are central nervous system, skin, lungs, kidneys and adrenals; bone marrow involvement may also occur.

##### Immunophenotype

B-cell associated antigens positive (CD19, CD20), CD30+/-, CD5-/+

##### Coding rules

Code *soft tissues* topographic site (C49.9).

#### 5.7.14. Primary effusion lymphoma M-9678/3

##### Definition

Primary effusion lymphoma is neoplasm of large B-cells that infiltrate serous cavities without forming tumour masses. The condition is closely associated with human herpes virus 8 (HHV-8) and EBV co-infection, typically in immunodeficient subjects.

##### Immunophenotype

s-Ig-/+ , c-Ig-/+ , CD45+/- , B-lineage markers (CD19, CD20) usually negative, CD30+/- , CD38+/- , CD138+/- , HHV8/KSHV-associated latent protein +

##### Main diagnostic criteria

1. Cytology of pleural, pericardial or peritoneal effusions shows infiltration by large B lymphocytes;
2. Pleural, pericardial or peritoneal biopsy shows infiltration by large B lymphocytes.

##### Coding rules

1. ICD-O-3 topography
  - pleura: C38.4
  - pericardium: C38.0
  - peritoneum: C48.2
2. Primary effusion lymphoma does not transform.

#### 5.7.15. Burkitt lymphoma/leukaemia M-9687/3 9826/3

##### Definition

Burkitt lymphoma is an aggressive disease characterized by fast (short doubling time) proliferation of medium-sized monomorphous transformed B-cells. The disease often presents at extranodal sites or as an acute leukaemia (M-9826/3). The leukaemic form is equivalent to the acute lymphocytic leukaemia-L3 (ALL-L3) of the old FAB classification and tends to involve the CNS at an early stage. All forms have a tendency to involve the CNS. Most (but not all) cases of Burkitt lymphoma are associated with c-myc rearrangement, as a result of t(8;14), or less commonly t(2;8) or t(8;22) translocations.

##### Subtypes

1. Endemic form of equatorial Africa and Papua-New Guinea, strongly associated with EBV. The mandible and other facial bones are typically affected; occurs mainly in children.
2. Sporadic form occurs throughout the world, again mainly in children, but with low incidence (1-2% of lymphomas in Western Europe and the USA<sup>5</sup>).
3. Immunodeficiency-associated variant related to HIV infection.

*Variants* Burkitt lymphoma with plasmacytoid differentiation, atypical Burkitt/Burkitt-like lymphoma

*Immunophenotype*

s-IgM+, CD10+, Bcl-6+, CD5-, CD23-, TdT-, Bcl-2-(-/+), very high proliferation rate (Ki-67 nearly 100%).

*Main diagnostic criteria*

1. Lymph node or tissue biopsy shows proliferation of medium-sized B lymphocytes with characteristic basophilic cytoplasm containing numerous vacuoles.
2. Cytogenetics shows one of three types of translocations, all involving the myc gene on chromosome 8: t(8;14), t(8;22) or t(2;8).
3. Molecular biology shows myc rearrangement.
4. Marrow aspirate/biopsy shows <20% marrow blasts.

*Coding rules*

1. The WHO and ICD-O-3 classifications no longer distinguish between Burkitt lymphoma and Burkitt leukaemia<sup>4,5</sup>. However the ICD-O-3 retains separate codes for lymphoma (9687/3) and leukaemia (9626/3). The recommendation is that these entities be treated together in future analyses, but that separate codes be retained to make it possible to perform comparative analyses compatible with past data. The two entities are distinguished as follows:  
Burkitt leukaemia (M-9826/3):
  - mainly marrow involvement
  - marrow blasts >20%.
 Burkitt lymphoma (M-9687/3).
  - mainly lymph node involvement
  - marrow blasts <20%.
2. Burkitt lymphoma does not transform.

**5.8. Mature T-cell and NK-cell neoplasms**

T and NK cells share functional and immunophenotypic characteristics and mature T-cell and NK-cell neoplasms are grouped together in the WHO and ICD-O-3 classifications<sup>4,5</sup>.

**5.8.1. Prolymphocytic leukaemia T-cell type** **M-9834/3***Definition*

Prolymphocytic leukaemia T-cell type is a rare aggressive disease characterized by proliferation of small-to-medium sized prolymphocytes that involve bone marrow, peripheral blood, lymph nodes, spleen, liver and skin.

*Immunophenotype*

CD2+, CD3+, CD7+, CD4+, CD8+/-

*Main diagnostic criteria*

Blood count: prolymphocytes (large atypical lymphoid cells with large nucleolus) >55% of all lymphocytes (generally >100,000 mm<sup>3</sup>).

*Coding rules*

T-cell prolymphocytic leukaemia does not transform.

**5.8.2. T-cell large granular lymphocytic leukaemia** **M-9831/3***Definition*

T-cell large granular lymphocytic leukaemia (T-LGL) is characterised by a persistent increase (>6 months) in the number of large granular peripheral blood lymphocytes.

*Immunophenotype*

CD3+, CD4-/+ , CD8+/- , CD57+/- , CD56-/+.

*Main diagnostic criteria*

Blood count shows granular lymphocytes >2 x10<sup>9</sup>/L.

*Coding rules*

1. T-LGL has behaviour code /1 in the ICD-O-3 classification and /3 in the WHO classification. This disease must be registered.
2. Staging for T-LGL does not follow the Ann-Arbor system, since no stage is discernible.
3. T-LGL does not transform.

**5.8.3. Aggressive NK-cell leukaemia** **M-9948/3***Definition*

Rare diseases characterised by proliferation of NK cells.

*Immunophenotype*

CD2+, CD3-, CD56+

*Main diagnostic criteria*

1. Smear shows presence of NK cells in peripheral blood.
2. Presence of cytotoxic markers granzyme B, TIA-i, and perforins.

*Coding rules*

1. *T/NK-cell leukaemia* is an NK-cell leukaemia and must be coded as such, i.e: M-9948/3.
2. Aggressive NK-cell leukaemia does not transform.
3. The immunophenotype of aggressive NK-cell leukaemia is identical to that of NK/T-cell lymphoma, nasal type: they are likely to be leukaemic and lymphomatous forms, respectively, of a single entity.

**5.8.4. Adult T-cell leukaemia/lymphoma HTLV1 positive** **M-9827/3***Definition*

Adult T-cell leukaemia/lymphoma HTLV1 positive (ATLL) is a neoplasm of activated mature T-lymphocytes



associated with infection by human T-cell leukaemia retrovirus, type 1 (HTLV-1).

#### *Immunophenotype*

CD2+, CD3+, CD4+, CD5+

#### *Main diagnostic criteria*

1. Blood smear or marrow aspirate shows *flower cells* – lymphocytes with polylobated nuclei.
2. Serum analysis shows HTLV-1 positivity in all cases.

#### *Coding rules*

1. Four forms of ATLL are recognised: acute, subacute, chronic, and lymphomatous. Whatever form is noted in clinical or pathological records, the code is always the same: M-9827/3.
2. ATLL may change from a chronic/subacute/lymphomatous form to acute disease. This is not a real transformation however.
3. Since ATLL is an HTLV-1-linked disease, the term *subacute* is still available for characterising the condition; however subacute is no longer to be used for characterizing other types of leukaemia.
4. Although an HTLV-1-linked entity, ATLL is a specific and distinct disease, differing from other T-cell lymphomas/leukaemias. Cancer registries are urged to guard against incorrect classification of this entity.

### **5.8.5. NK/T-cell lymphoma, nasal type M-9719/3**

#### *Definition*

Nasal type extranodal NK/T-cell lymphoma almost always presents with nasal localization. It is usually associated with Epstein-Barr virus EBV.

#### *Immunophenotype*

CD2+, CD3-, CD56+

#### *Main diagnostic criteria*

1. Tissue biopsy shows diffuse infiltration by T/NK lymphocytes, often accompanied by injury of small blood vessels.
2. Granzyme B, TIA-i, and perforins (enzymes with cytotoxic properties) present.
3. EBV positivity in over 90% of cases.

#### *Coding rules*

1. Extranodal NK/T-cell lymphoma, nasal type has a nasal localisation in most cases. If the disease arises at another site (skin, soft tissues, gastrointestinal tract, testis) it is still considered nasal type.
2. Extranodal NK/T-cell lymphoma, nasal type, does not transform.

### **5.8.6. Enteropathy-associated T-cell lymphoma (Intestinal T-cell lymphoma)**

**M-9717/3**

#### *Definition*

Intestinal T-cell lymphoma is a neoplasm of intraepithelial lymphocytes, usually localized in the jejunum or ileum, more rarely stomach, duodenum, colon, or extra intestinal sites.

#### *Immunophenotype*

CD3+, CD5-, CD7+, CD4-, CD8 +/-, CD30+/-

#### *Main diagnostic criteria*

Biopsy of intestinal wall shows infiltration of neoplastic T-lymphocytes in association with variable signs of enteropathy.

#### *Coding rules*

1. Enteropathy-type T-cell lymphoma does not transform.
2. The usual localization is jejunum and ileum.

### **5.8.7. Hepatosplenic $\gamma\delta$ -cell lymphoma M-9716/3**

#### *Definition*

Hepatosplenic  $\gamma\delta$ -cell lymphoma is a rare extranodal lymphoma arising from cytotoxic T-lymphocytes usually of  $\gamma\delta$  type. The terms  $\alpha\beta$  and  $\gamma\delta$  refer to two possible structures of the T-cell receptor (TCRs). T-cell lymphomas usually express  $\alpha\beta$  type TRCs, but in this disease the  $\alpha\beta$  type occurs in only a minority of cases. Hepatosplenic  $\gamma\delta$ -cell lymphoma usually involves spleen, liver and bone marrow.

#### *Immunophenotype*

CD3+, CD4-, CD5-, CD8+, CD56+/-.

#### *Main diagnostic criteria*

1. Tissue biopsy shows presence of  $\gamma\delta$  lymphocytes.
2. Molecular biology shows  $\gamma\delta$  structure for TCR.

#### *Coding rules*

1. Topography:
  - with hepatosplenic localization, code the involved organ (e.g., liver C22.0);
  - if bone marrow is involved (common), in association with hepatosplenic localization, code the involved organ (e.g., liver C22.0);
  - for bone marrow and multivisceral involvement, code the marrow site (C42.1);
  - for multivisceral localization without bone marrow involvement: code C77.8 (lymph nodes of multiple regions).
2. Hepatosplenic  $\gamma\delta$ -cell lymphoma does not transform.

### 5.8.8. Subcutaneous panniculitis-like T-cell lymphoma **M-9708/3**

#### Definition

Subcutaneous panniculitis-like T-cell lymphoma is a cytotoxic T-cell lymphoma that preferably infiltrates subcutaneous tissue.

#### Immunophenotype

CD3+, CD8+

#### Main diagnostic criteria

1. Skin biopsy shows proliferation of neoplastic T-lymphocytes in subcutaneous tissue, with sparing of epidermis and dermis.
2. Granzyme B, TIA-i, and perforins (cytotoxic markers) present.

#### Coding rules

1. The trunk (C49.3, C49.6) or extremities (C49.1, C49.2) are the main subcutaneous sites.
2. Subcutaneous panniculitis-like T-cell lymphoma does not transform.
3. The Ann Arbor staging system is not used for subcutaneous/cutaneous lymphomas.

### 5.8.9. Mycosis fungoides; Sézary syndrome **M-9700/3; M-9701/3**

#### Definition

Mycosis fungoides (MF) is a lymphoma of small-to-medium sized mature T-cells that infiltrate dermis and epidermis. Sézary syndrome (SS) is a similar but rarer condition, with localisation in peripheral blood or bone marrow.

#### Immunophenotype

CD2+, CD3+, CD4+, CD5+, CD8-, CD14+

#### Main diagnostic criteria

1. For MF: skin biopsy shows proliferation of neoplastic small, mature T-lymphocytes in dermis and epidermis.
2. For SS: blood smear shows Sézary cells (neoplastic T-lymphocytes).

#### Coding rules

1. MF is always assigned behaviour code /3 even though it is often an indolent disease requiring differential diagnosis against non-tumoral diseases such as inflammatory infiltrates (eczema) and pseudolymphoma (especially after post-treatment), rather than other lymphomas. Serial skin biopsies may not afford a clear diagnosis. Clinical characteristics, such as appearance of skin patches, plaques and eventually tumours, and response to chemotherapy, are important for securing the diagnosis. Therefore

clinical data must be always consulted together with the pathological report.

2. SS is a disseminated disease characterised by erythroderma and generalized lymphadenopathy; whereas MF is primarily a skin disease.
3. Sézary cells may be present in peripheral blood during MF but the diagnosis remains MF. MF does not transform into SS.
4. MF may become *transformed MF*; however transformed MF is not present in ICD-O-3 classification and should not be registered.
5. MF also includes the variant pagetoid lymphoma (pagetoid syndrome).
6. The term *pre-mycosis* should not be used. An early stage MF must be coded as MF.
7. The term *en plaque para psoriasis* is no longer used. Such entities are considered early MF and must be coded as MF.
8. For MF (and other cutaneous lymphomas) the Ann Arbor staging system is not used.

### 5.8.10. Primary cutaneous anaplastic large cell lymphoma (Primary cutaneous CD30-positive T-cell lymphoproliferative disorders) **M-9718/3**

#### Definition

Primary cutaneous anaplastic large cell lymphomas is a CD30-positive T-cell lymphoma presenting in skin.

#### Immunophenotype

CD3-, CD4+, CD30+, ALK-

#### Main diagnostic criteria

Skin biopsy shows infiltration of dermis and subcutaneous tissue by large T lymphoid cells.

#### Coding rules

1. A B-cell anaplastic lymphoma, CD30+, with cutaneous localization must be coded as C44.0; M-9680/3 (malignant lymphoma large B cell, diffuse).
2. CD30+ cutaneous lymphomas include:
  - Cutaneous anaplastic T-cell lymphoma, CD30+, which differs from *anaplastic large cell lymphoma T-cell and null-cell type CD30+* (M-9714/3) because of its predominantly cutaneous localization.
  - Lymphomatoid papulosis.
3. The Ann Arbor staging system is not used for cutaneous lymphomas.

### 5.8.11. Cutaneous T-cell lymphoma, NOS **M-9709/3**

#### Definition

The diagnosis of cutaneous T-cell lymphoma NOS is only assigned when the pathologist cannot reach a more specific diagnosis.

*Immunophenotype*

T-cell markers.

*Main diagnostic criteria*

Skin biopsy shows proliferation of neoplastic cutaneous T-lymphocytes. Cutaneous T-cell lymphoma NOS is only diagnosed after exclusion of other similar diseases and has no specific diagnostic criteria.

*Coding rules*

1. This diagnosis reveals that the pathologist was unable to more precisely specify the disease often due to low quality biopsy samples.
2. For cutaneous lymphomas the Ann Arbor staging system is not used.

### 5.8.12. Angioimmunoblastic T-cell lymphoma M-9705/3

*Definition*

Angioimmunoblastic T-cell lymphoma is a peripheral neoplasm characterised by systemic disease, polymorphous infiltrate of lymph nodes and high endothelial venules, and follicular cell proliferation.

*Immunophenotype*

CD3+, CD4+, CD8+/-

*Main diagnostic criteria*

Lymph-node or tissue biopsy shows polymorphous neoplastic T-lymphocytes and other cell types (B-lymphocytes, eosinophilic granulocytes, plasma cells, histiocytes, dendritic follicular cells) associated with proliferation of small blood vessels.

*Coding rules*

1. The ICD-O-3 assigns angioimmunoblastic lymphadenopathy behaviour code /1, but is considered malignant by the WHO (2008)<sup>5</sup>. This entity must be registered as *angioimmunoblastic T-cell lymphoma* and coded as M-9705/3.
2. Angioimmunoblastic T-cell lymphoma does not transform.

### 5.8.13. Peripheral T-cell lymphoma, NOS (Mature T-cell lymphoma, NOS) M-9702/3

*Definition*

Unspecified peripheral T-cell lymphomas are a large group of mainly nodal (but also extranodal) mature T-cell lymphomas that cannot be better specified. The

term *peripheral* indicates that the T-cells mature after leaving bone marrow.

*Immunophenotype*

CD3+, CD4+, CD8+/-, TCR αβ or γδ.

*Main diagnostic criteria*

Lymph-node or tissue biopsy shows proliferation of mature T-lymphocytes.

*Coding rules*

Peripheral T-cell lymphoma does not transform.

### 5.8.14. Anaplastic large cell lymphoma, T-cell and null cell type (ALCL) M-9714/3

*Definition*

Anaplastic lymphoma of T-cell or null cell type that is positive for anaplastic lymphoma kinase (ALK).

*Immunophenotype*

CD30+, ALK+

*Main diagnostic criteria*

1. Lymph-node or tissue biopsy shows proliferation of large anaplastic cells.
2. Cytogenetics often shows t(2;5) translocation.

*Coding rules*

1. Only anaplastic T-cell/null-cell lymphomas are included: anaplastic lymphomas with B-cell phenotype are coded M-9680/3.
2. Anaplastic lymphomas are not subject to transformation.

## 5.9. Hodgkin lymphoma

Hodgkin lymphomas (HL) share the following characteristics: usually arise in lymph nodes; usually occur in young adults; neoplastic tissues contain small numbers of Hodgkin and Reed-Sternberg cells in an abundant matrix of inflammatory and non-neoplastic cells. There are two main types of HL: nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (CHL). However several subtypes of CHL have been recognised by the WHO and ICD-O-3 (Table 5.9.1.)<sup>4,5</sup>.

The neoplastic lymphoid cells have been identified as B-cells. However, because HL differs in terms of incidence, clinical presentation and prognosis from other B-cell neoplasms, it is considered separately from other mature B-cell lymphomas.

**Table 5.9.1. - Sub-classification of Hodgkin lymphomas**

Categories	ICD-O-3 code	WHO recommended code
Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)	M-9659/3	M-9659/3
Classical Hodgkin lymphoma NOS (CHL)	M-9650/3	M-9650/3
<i>Subtypes of Classical Hodgkin lymphoma</i>		
Nodular sclerosis Hodgkin lymphoma (NSHL)	M-9663/3	M-9663/3
Nodular sclerosis Hodgkin lymphoma cellular phase	M-9664/3	M-9663/3
Nodular sclerosis Hodgkin lymphoma grade 1	M-9665/3	M-9663/3
Nodular sclerosis Hodgkin lymphoma grade 2	M-9667/3	M-9663/3
Mixed cellularity Hodgkin lymphoma (MCHL)	M-9652/3	M-9652/3
Lymphocyte rich classical Hodgkin lymphoma (LRCHL)	M-9651/3	M-9651/3
Lymphocyte depleted Hodgkin lymphoma (LDHL)	M-9653/3	M-9653/3
Lymphocyte depleted Hodgkin lymphoma with diffuse fibrosis	M-9654/3	M-9653/3
Lymphocyte depleted Hodgkin lymphoma, reticular	M-9655/3	M-9653/3
Hodgkin granuloma (obsolete)	M-9661/3	M-9650/3
Hodgkin sarcoma (obsolete)	M-9662/3	M-9650/3

**Table 5.9.2. - Immunophenotypes of Hodgkin lymphomas**

Marker	NLPHL	CHL
CD30	-	+
CD15	-	+/-
CD45	+	-
CD20	+	-/+
CD79a	+	-/+

**Main diagnostic criteria**

Biopsy shows presence of Reed-Sternberg cells.

**Coding rules**

- Only the seven categories of the WHO classification (NLPHL, CHL, NSHL, MCHL, LRCHL, LDHL, and Hodgkin granuloma) are of interest for coding purposes. The 13 categories of ICD-O-3 are condensed, in Table 5.9.1, into the seven WHO categories.
- If the pathological report comes with a diagnosis of:
  - Hodgkin granuloma: code M-9650/3 (Table 5.9.1.)
  - Hodgkin paraganuloma: code M-9659/3 (i.e., NLPHL)

- If HL and non-Hodgkin lymphoma are noted as being present in a single patient (can occur even in pathological reports) and there is no definitive decision as to which disease is present, then code M-9590/3 (malignant lymphoma NOS).
- Nodular lymphocyte predominant Hodgkin lymphoma NLPHL (M-9659/3) is also known as *Paraganuloma of Poppema-Lennert*; it is a fully distinct entity and must be coded separately from classical Hodgkin lymphoma (M-9650/3): these two entities must be distinguished from each other and other Hodgkin lymphomas in data analyses and publications.
- The term *Hodgkin disease* is no longer recommended; according to the ICD-O-3 the preferred term is *Hodgkin lymphoma*.
- Classical Hodgkin lymphomas are not subject to transformation.
- In nodular lymphocyte predominant Hodgkin lymphoma (M-9659/3) progression to large B-cell lymphoma-like lesions has been reported in approximately 3-5% of cases.



## 6. Mast cell tumours

Mast cells are derived from haematopoietic progenitors and are involved in inflammatory and allergic reactions. Mast cell tumours are rare entities that proliferate and localize in several organs and have highly variable clinical course, ranging from self-limiting skin lesions (in 80% of patients skin is the only site) to aggressive disease with systemic involvement and poor prognosis. Anaemia, leukocytosis or leucopenia, thrombocytosis or thrombocytopenia often go with the evolution of the disease. Although mast cell tumours may occur at any age, they have a biphasic incidence curve, being seen most often in children and in adults in the third and fourth decades of life.

### Immunophenotype

CD2+, CD25+, CD45+, CD68+, CD177+, Cd14-, CD15, CD16-; B and T markers negative.

### Classification and diagnostic criteria

- Mast cell sarcoma: M-9740/3  
Extremely rare neoplasm characterized by localised

infiltration of highly atypical neoplastic mastocytes. Distant spread and a leukaemic phase are also possible.

- Malignant (systemic) mastocytosis: M-9741/3  
Tumour with multifocal localizations (extra-cutaneous sites, bone marrow).
- Mast cell leukaemia (MCL): M-9742/3  
Bone marrow aspirate/biopsy shows  $\geq 20\%$  mastocytes.

### Coding rules and comments

1. Cutaneous mastocytosis (M-9741/1) and extracutaneous mastocytoma (M-9740/1) are not malignant and must not be registered.
2. Malignant (systemic) mastocytosis (M-9741/3) may have a cutaneous localisation, but bone marrow or extracutaneous involvement is required to secure the diagnosis.
3. Mast cell sarcoma (M-9740/3) cannot be associated with bone marrow or skin involvement.
4. Malignant (systemic) mastocytosis can be associated with another haemopathy.

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## 8. The HAEMACARE grouping

Table 8.1. - HAEMACARE Study Group proposal for grouping haematological malignancies (July 2009) according to their morphology (ICD-O-3 codes)

ICD-O-3 Description	HAEMACARE group number	ICD-O-3 Morphology Code	Morphology description in clear
Lymphoma, NOS	1	9590	Malignant lymphoma, NOS
NH lymphoma, NOS	2	9591	Malignant lymphoma, non-Hodgkin, NOS
Composite Hodgkin and non-Hodgkin lymphoma	3	9596	Composite Hodgkin and non-Hodgkin lymphoma
Hodgkin lymphoma, nodular lymphocyte predominance	4	9659	Hodgkin lymphoma, nodular lymphocyte predominance
Classical HL, NOS	5	9650	Hodgkin lymphoma, NOS
	5	9661	Hodgkin granuloma [obs]
	5	9662	Hodgkin sarcoma [obs]
Classical HL, lymphocyte rich	5	9651	Hodgkin lymphoma, lymphocyte-rich
Classical HL, nodular sclerosis	5	9663	Hodgkin lymphoma, nodular sclerosis, NOS
	5	9664	Hodgkin lymphoma, nodular sclerosis, cellular phase
	5	9665	Hodgkin lymphoma, nodular sclerosis, grade 1
	5	9667	Hodgkin lymphoma, nodular sclerosis, grade 2
Classical HL, mixed cellularity	5	9652	Hodgkin lymphoma, mixed cellularity, NOS
Classical HL, lymphocyte depletion	5	9653	Hodgkin lymphoma, lymphocyte depletion, NOS
	5	9654	Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis
	5	9655	Hodgkin lymphoma, lymphocyte depletion, reticular
Chronic lymphocytic leukaemia/ Small lymphocytic lymphoma	6	9670	Malignant lymphoma, small B lymphocytic, NOS
	6	9823	B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma
Immunoproliferative diseases	7	9760	Immunoproliferative disease, NOS
	7	9671	Malignant lymphoma, lymphoplasmacytic
	7	9761	Waldenström macroglobulinemia
	7	9762	Heavy chain disease, NOS
Mantle cell / centrocytic	8	9673	Mantle cell lymphoma
Follicular B lymphoma	9	9690	Follicular lymphoma, NOS
	9	9691	Follicular lymphoma, grade 2
	9	9695	Follicular lymphoma, grade 1
	9	9698	Follicular lymphoma, grade 3

ICD-O-3 Description	HAEMACARE group number	ICD-O-3 Morphology Code	Morphology description in clear
Diffuse B lymphoma	10	9675	Malignant lymphoma, mixed small and large cell, diffuse [obs]
	10	9678	Primary effusion lymphoma
	10	9679	Mediastinal large B-cell lymphoma
	10	9680	Malignant lymphoma, large B-cell diffuse, NOS
	10	9684	Malignant lymphoma, large B-cell, diffuse, immunoblastic, NOS
Burkitt's	11	9687	Burkitt lymphoma, NOS
	11	9826	Burkitt cell leukaemia
Marginal zone lymphoma	12	9689	Splenic marginal zone, B-cell lymphoma
	12	9699	Marginal zone B-cell lymphoma, NOS/MALT lymphoma
	12	9764	Immunoproliferative small intestinal disease (Mediterranean lymphoma)
T lymphoma cutaneous	13	9700	Mycosis fungoides
	13	9701	Sézary syndrome
	13	9709	Cutaneous T-cell lymphoma, NOS
	13	9718	Primary cutaneous CD30 positive T cell lymphoproliferative disorder
	13	9708	Subcutaneous panniculitis-like T-cell lymphoma
Other T cell lymphomas	14	9702	Mature T-cell lymphoma
	14	9705	Angioimmunoblastic T-cell lymphoma
	14	9714	Anaplastic large cell lymphoma, Tcell and Null cell type
	14	9716	Hepatosplenic $\gamma\delta$ -cell lymphoma
	14	9717	Intestinal T-cell lymphoma
	14	9948	Aggressive NK-cell leukaemia
	14	9719	NK/T cell lymphoma, nasal type
	14	9827	Adult T-cell leukaemia/lymphoma (HTLV-1 positive)
	14	9831	T-cell large granular lymphocytic leukaemia
	14	9834	Prolymphocytic leukaemia, T-cell type
Lymphoblastic lymphoma/Acute (precursor cell) lymphatic leukaemia	15	9727	Precursor cell lymphoblastic lymphoma, NOS
	15	9728	Precursor B- cell lymphoblastic lymphoma
	15	9729	Precursor T-cell lymphoblastic lymphoma
	15	9835	Precursor cell lymphoblastic leukaemia, NOS
	15	9836	Precursor B-cell lymphoblastic leukaemia
	15	9837	Precursor T-cell lymphoblastic leukaemia

ICD-O-3 Description	HAEMACARE group number	ICD-O-3 Morphology Code	Morphology description in clear
Plasma cells neoplasms	16	9731	Plasmacytoma, NOS
	16	9734	Plasmacytoma, extramedullary
	16	9732	Multiple myeloma
	16	9733	Plasma cell leukaemia
Mature B cell leukaemia	17	9833	Prolymphocytic leukaemia, B-cell type
Mature B cell leukaemia, hairy cell	18	9940	Hairy cell leukaemia
Lymphatic leukaemia, NOS	19	9820	Lymphoid leukaemia, NOS
	19	9832	Prolymphocytic leukaemia, NOS
Leukaemia, NOS	20	9800	Leukaemia, NOS
	20	9801	Acute leukaemia, NOS
	20	9805	Acute biphenotypic leukaemia
Myeloid leukaemia, NOS	21	9860	Myeloid leukaemia, NOS
Acute myeloid leukaemia	22	9840	Acute myeloid leukaemia, M6 type
	22	9861	Acute myeloid leukaemia, NOS
	22	9867	Acute myelomonocytic leukaemia
	22	9870	Acute basophilic leukaemia
	22	9872	Acute myeloid leukaemia minimal differentiation
	22	9873	Acute myeloid leukaemia, without maturation
	22	9874	Acute myeloid leukaemia with maturation
	22	9891	Acute monocytic leukaemia
	22	9910	Acute megakarioblastic leukaemia
	22	9930	Myeloid sarcoma
	22	9866	Acute promyelocytic leukaemia
	22	9871	Acute myeloid leukaemia with abnormal marrow eosinophils
	22	9896	Acute myeloid leukaemia, t(8,21) (q22,q22)
	22	9897	Acute myeloid leukaemia, 11q23 abnormalities
	22	9895	Acute myeloid leukaemia, with multilineage dysplasia
	22	9984	Refractory anaemia with excess blasts in transformation [obs]
	22	9920	Therapy-related acute myeloid leukaemia, NOS
	22	9987	Therapy-related myelodysplastic syndrome, NOS
	22	9931	Acute panmyelosis with myelofibrosis

ICD-O-3 Description	HAEMACARE group number	ICD-O-3 Morphology Code	Morphology description in clear
<b>Myeloproliferative neoplasms</b>	23	9740	<b>Mastocytoma, NOS/mast cell sarcoma</b>
	23	9741	<b>Malignant mastocytosis</b>
	23	9742	<b>Mast cell leukaemia</b>
	23	9863	<b>Chronic myeloid leukaemia, NOS</b>
	23	9875	<b>Chronic myelogenous leukaemia, BCR/ABL 1 positive</b>
	23	9950	<b>Polycythemia vera</b>
	23	9961	<b>Myelosclerosis with myeloid metaplasia</b>
	23	9962	<b>Essential thrombocythemia</b>
	23	9963	<b>Chronic neutrophilic leukaemia</b>
	23	9964	<b>Hypereosinophilic syndrome</b>
	23	9960	<b>Chronic myeloproliferative disease, NOS</b>
<b>Myelodysplastic syndrome</b>	24	9980	<b>Refractory anaemia</b>
	24	9982	<b>Refractory anaemia with sideroblasts</b>
	24	9983	<b>Refractory anaemia with excess blasts</b>
	24	9985	<b>Refractory cytopenia with multilineage dysplasia</b>
	24	9986	<b>Myelodysplastic syndrome 5q deletion (5q-) syndrome</b>
	24	9989	<b>Myelodysplastic syndrome, NOS</b>
<b>Myelodysplastic/Myeloproliferative neoplasms</b>	25	9945	<b>Chronic myelomonocytic leukaemia</b>
	25	9876	<b>Atypical chronic myeloid leukaemia, BCR/ABL-1 negative</b>
	25	9946	<b>Juvenile myelomonocytic leukaemia</b>
	25	9975	<b>Myeloproliferative/myelodysplastic neoplasm, unclassifiable</b>

NB The different "nuances" within the same large group suggest the entity or the subgroup that could be subject to detailed analysis.