



CHAPTER 4

Specific tumor sites (part 3)

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CHAPTER 4

Specific tumor sites (part 3)

Lymphohematopoietic cancer

In the light of the new classifications, the ICD-O-3 coding system has introduced relevant changes for these diseases compared to previous editions. It also added an important new group of cancerous diseases: chronic myeloproliferative disorders and chronic myelodysplastic disorders, also known as “myelodysplastic syndromes.” A careful study and review of all registration problems arising from the new codes is therefore required. Since hematological neoplasms are very various and inhomogeneous, they must be studied case by case in detail.

The ICD-O also codes the site of many hematological diseases as C42 (hematopoietic and reticuloendothelial systems, a code vacant in ICD-10). The following are the subcategories of C42: C42.0: blood; C42.1: bone marrow; C42.2: spleen; C42.3: reticuloendothelial system, NOS; C42.4: hematopoietic system, NOS

Obviously, all lymph node or parenchymal sites have their own codes.

For some hematological neoplasms, the site within C42 is pre-established and mandatory.

Lymphomas

Disease classifications

Lymphomas, as all hematologic cancers, involve the entire lymphohematopoietic system, i.e., by definition they are multicentric tumors that can appear in and then spread through any organ or system of the body. Therefore for registration purposes they cannot be considered as other solid tumors that as a rule have a primary site and may have one or more metastatic sites: since the TNM system is not used to stage these tumors.

Their spreading in the human body is classified in stages (I, II, III and IV). Consequently, from a strictly nosological point of view, instead of **metastases** the term **locations** is used when describing lymphomas. Thus the site assigned during registration can vary greatly; it is almost always the site of first onset or, in any case, the site most involved at the time of diagnosis. Classification of lymphoma, due to its polymorphism, can be complicated by nosographic problems, for instance compared to hematological cancers that are apparently very different, such as some types of leukemia. In this sense, today the principle that chronic lymphocytic leukemia (CLL) is in most cases actually a low grade small B-cell non-Hodgkin's lymphoma is finally accepted. It may receive two

different nosographic terms only because it can present clinically in two different ways, but it is actually the same disease.

Lymphomas are defined with codes from 9590 to 9729 of ICD-O-3: detailed analysis, with the corresponding ICD-9 and ICD-10 codes, makes it possible to identify a number of groups (the codes mentioned below are all considered with behavior /3).

Malignant lymphoma (diffuse), NOS; Non-Hodgkin's lymphoma (diffuse), NOS M-9590-9596 (ICD-9: 202.8, 200.0, 200.1, 200.8; ICD-10: C85.9, C82.9, C83.9: *these are the non-specific Lymphoma, NOS or Non-Hodgkin's lymphoma, NOS codes, which can be used for cases with low diagnostic quality and clinical definition. Code M-9596 is a very unusual occurrence, as discussed with respect to multiple hematologic cancers*).

When diagnosis is based solely on non histological examinations (diagnostic imaging, clinical assessment), or if the case is DCO, Lymphoma, NOS M-9590/3 must be used, following the 1999 IARC rule.

Hodgkin's lymphoma, NOS M-9650-9667

(ICD-9: from 201.0 to 201.9; ICD-10: from C81.0 to C81.9)

It does not usually present particular registration problems, except perhaps due to the fact that it is almost always diagnosed and treated outside a hospital setting, and therefore it is seldom found documented in HDDs.

Mature B-cell non-Hodgkin's lymphoma M-9670-9699

◆ Small B-cell lymphocytic lymphoma M-9670 (ICD-9: 200.1; ICD-10: C83.0)

In ICD-O-3 it is explicitly correlated, among leukemias, to code M-9823 (ICD-9: 204.1;- ICD-10: C91.1), which identifies CLL, Chronic lymphocytic leukemia; in practice the two diseases make up a single pathologic entity.

◆ Lymphoplasmacytic, plasmacytoid, lymphoplasmacytoid lymphoma; immunocytoma M-9671 (ICD-9: 200.8; ICD-10: C83.8)

It, too, is correlated, within the field of immunoproliferative disorders, to code M-9761 (ICD-9: 273.3; ICD-10: C88.0) which is the code for Waldenström's

macroglobulinemia, with which in practice it makes up a single pathologic entity.

- ◆ **Mantle cell lymphoma M-9673** (*ICD-9: 200.1; ICD-10: C83.8*)

This is the most common nosographic term today, although a number of synonyms exist. It is a low grade (but sometimes high grade) lymphoma, which accounts for about 5% of NH lymphomas and is very often correlated to certain immunohistological and genetic characteristics, such as translocation t(11;14).

- ◆ **Malignant lymphoma, mixed small and large cell, diffuse; centroblastic-centrocytic, diffuse; mixed lymphohistiocytic, diffuse M-9675** (*ICD-9: 200.8, 202.8; ICD-10: C83.2*)

It is a low grade lymphoma, correlated to M-9690, which is likely its follicular form. Codes 9675 and 9690 can therefore represent a single pathologic entity and, within the context of NH lymphomas, could be merged in a single category.

- ◆ **Primary effusion lymphoma M-9678 and mediastinal (thymic) large B-cell lymphoma M-9679** (*ICD-9: 202.8; ICD-10: C85.7*)

The former must be assigned to the serous cavity (pleura, peritoneum) the latter to the mediastinum or thymus.

- ◆ **Malignant lymphoma, large B-cell, diffuse, NOS M-9680** (*ICD-9: 200.0, 200.1; ICD-10: C83.3*)

This high grade lymphoma is perhaps the most frequent B-cell lymphoma. It is also termed “centroblastic, diffuse”, “histiocytic”, “large B-cell, anaplastic”, “large B-cell, T-cell rich,” etc. The ICD-O-3 manual offers a long, exhaustive list of synonyms, or histopathological locutions under this code, which accounts for about 30-40% of NH lymphomas.

- ◆ **Malignant lymphoma, large B-cell, diffuse, immunoblastic M-9684** (*ICD-9: 200.8; ICD-10: C83.4*)

Also known as Immunoblastic lymphoma, or sarcoma, or Plasmablastic lymphoma. It is a very high grade lymphoma, rarer than the previously listed type.

- ◆ **Burkitt's lymphoma M-9687** (*ICD-9: 200.2; ICD-10: C83.4*)

High grade, occurs in adults but also in children, frequently extranodal, it almost always present a particular immunohistological and genetic profile and is associated to several chromosomal abnormalities, as t(8;14), t(2;8), t(8;22). It is correlated to code M-9826 (*ICD-9: 204.0; ICD-10: C91.0*) which identifies Burkitt cell leukemia (or ALL-B, or FAB L3, or Acute lymphoblastic leukemia, mature B-cell type): within the group of NH lymphomas, these two codes can therefore make

up in practice a single pathologic entity. In any case, these diseases are relatively rare.

- ◆ **Splenic marginal zone B-cell lymphoma M-9689** (*ICD-9: 200.1; ICD-10: C83.4*)

Also known as Splenic lymphoma with villous lymphocytes, it is generally associated to bone marrow and peripheral blood involvement. Coding to the splenic site (C 42.2) is mandatory.

- ◆ **Follicular (nodular) or follicle center lymphoma M-9690, M-9691, M-9695, M-9698** (*ICD-9: 202.0; ICD-10: C82.0-C82.9*)

It also has different names. M-9690 is Follicular lymphoma, NOS; M-9695 is Follicular lymphoma grade 1; M-9691 is Follicular lymphoma grade 2; M-9698 is Follicular lymphoma grade 3. As mentioned previously, M-9690 is correlated to M-9675. Follicular lymphomas of grade 1 and 2 are low grade, while those of grade 3 are high grade. As previously mentioned, low grade follicular lymphomas are often treated and followed up outside a hospital setting; it must be therefore noted that there is often no trace of them in HDDs or when they are found in hospital admissions it is only in the presence of complicating conditions, thus hospitalization sources often do not reflect the true incidence of this lymphoma.

- ◆ **Marginal zone B-cell lymphoma, monocytoid B-cell lymphoma M-9699** (*ICD-9: CM 200.10-18; ICD-10: C85.7*)

Also commonly called Lymphoma of the mucosa-associated lymphoid tissue, or MALT lymphoma, or simply Maltoma: for other locations, it is also defined as Lymphoma of the bronchial-associated lymphoid tissue (or BALT lymphoma) and Lymphoma of the skin-associated lymphoid tissue (or SALT lymphoma). These lymphomas, fairly common and low grade, are usually extranodal; the typical site is the stomach (associated to gastritis from *Helicobacter pylori*), but they can also be present in the lung, thyroid, skin, salivary glands, breast, etc.; more rarely, it is a primary disease of the lymph nodes or lymphatic structures. Often they are diagnosed, treated, and followed up at the physician office.

STAGING OF MYCOSIS FUNGOIDES

- stage I:** a small amount of the skin surface is covered with patches and/or plaques
- stage II:** a moderate amount of the skin surface is covered with papules or plaques and usually associated to patches
- stage III:** formation of tumor nodes, usually associated to papules, plaques, or lesions
- stage IV:** one or more of the above in addition to enlarged lymph nodes
- stage V:** one or more of the above-described lesions associated with enlarged lymph nodes and visceral involvement

T and NK mature cell lymphomas M-9700-9719

 ◆ **Mycosis fungoides M-9700** (*ICD-9: 202.1; ICD-10: C84.0*)

As a T lymphoma of the skin, it must be coded to the site for skin (C44).¹ Along with Sézary's syndrome, Mycosis fungoides is also known as Post-thymic T-cell lymphoma of the skin, Small cell cerebriform lymphoma, or Epidermotrophic B-cell lymphoma. Although it is not a common disease, it is not altogether rare, especially in males between the sixth and seventh decade of age. Its behavior is prevalently that of a slow-growing chronic lymphoma, mostly low grade. It is usually diagnosed and cured (phototherapy, PUVA, REPUVA, etc.) outside a hospital setting, almost always by a dermatologist, so it often falls into the above-mentioned cases of outpatient incidence. In the light of its particular clinical features, it is staged quite differently from other lymphomas. Most cases are generally diagnosed in stages I-II.

 ◆ **Sézary's syndrome (or disease) M-9701** (*ICD-9: 202.2; ICD-10: C84.1*)

It is basically a leukemic variant of Mycosis fungoides. It presents as a chronic T-cell leukemia associated with erythroderma (see below, Lymphomas and Chronic lymphocytic leukemia). Considering the extreme pathogenetic and immunogenetic affinity of these two diseases, in NH lymphoma reports, codes 9700 and 9701 could be grouped as a single pathologic entity.

 ◆ **Mature T-cell lymphoma, Peripheral T-cell or T-zone lymphoma M-9702** (*ICD-9: 202.8; ICD-10: C84.2, C84.3, C84.4*). Also known as Lennert's lymphoma, or Lymphoepithelioid lymphoma This group of lymphomas is fairly heterogeneous and difficult to differentiate: basically, most T-cell lymphomas that have not yet received a more detailed histopathological, immunogenetic, and clinical-hematological definition (see codes below) are grouped under this code. They account for about 10-15 % of NH lymphomas; they can have lymph node locations, but extranodal sites are also fairly common. Though often presenting aggressively, they are usually considered curable, and therefore classified both with low grade and with high grade lymphomas.

 ◆ **Angioimmunoblastic T-cell lymphoma, Angioimmunoblastic lymphoma M-9705** (*ICD-9: 202.8; ICD-10: C84.4*). Also known as Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) or Immunoblastic lymphadenopathy (IBL), it is quite rare.

 ◆ **Subcutaneous panniculitis-like T-cell lymphoma M-9708 and Cutaneous T-cell**
lymphoma, NOS M-9709 (*ICD-9: 202.8; ICD-10: C84.5*)

Their site is evidently, as a rule, the skin (C44) and they are quite rare.

 ◆ **Anaplastic large cell lymphoma, of the B-cell and Null cell type M-9714** (*ICD-9: 200.1; ICD-10: C85.7*)

Also known as Large cell lymphoma (Ki-1+) or Anaplastic large cell lymphoma, CD30+; quite rare, it is a high grade lymphoma, presenting in nodal and extranodal sites, prevalently in youth. Many recent cases of this lymphoma have been observed to be correlated with HIV.

 ◆ **Hepatosplenic $\gamma\delta$ (gamma-delta) T-cell lymphoma M-9716** (*ICD-9: 202.8; ICD-10: C84.5*) Rare.

 ◆ **Intestinal T-cell lymphoma M-9717** (*ICD-9: 202.8; ICD-10: C84.1*)

Also known as T-cell lymphoma associated with enteropathy, it is a rare lymphoma in adults, almost always occurring in subjects with a history of gluten enteropathy.

 ◆ **Primary cutaneous CD30+ T-cell lymphoproliferative disorder M-9718** (*ICD-9: 202.8; ICD-10: C84.5*)

Also known as Lymphomatoid papillomatosis, or Primary cutaneous large B-cell lymphoma, anaplastic (or T-cell, CD30+), it is a rare lymphoma arising from the skin (site code C44).

 ◆ **Nasal and nasal type NK/T-cell lymphoma M-9719** (*ICD-9: 202.3; ICD-10: C85.7*)

A rare lymphoma, also known as Angiocentric B-cell lymphoma, Malignant reticulosis, Polymorphic reticulosis, or Midland malignant reticulosis, it almost always has extranodal presentation mainly involving nose, palate, or skin. This disease is probably the malignant evolution of Lymphoid granulomatosis, or Angiocentric immunoproliferative lesion (9766/1, see immunoproliferative disorders).

Precursor cell lymphoblastic lymphoma, M-9727-9729

 ◆ **Precursor lymphoblastic lymphoma, NOS M-9727** (*ICD-9: 200.1; ICD-10: C83.5*). Also known as Lymphoblastoma or Malignant convoluted cell lymphoma. This code is also suited for Lymphoblastic lymphoma, NOS cases, i.e., in which the B- or T-cell phenotype is not defined. These are high grade lymphomas, that account for less than 5% of NHLs, typical of youth, with frequent involvement of the central nervous system and of the bone marrow. Code M-9727 is explicitly correlated to M-9835 (*ICD-9 CM: 204.00-01; ICD-10: C91.0*), which corresponds to Precursor cell lymphoblastic leukemia

NOS, or Acute lymphoblastic leukemia, or Acute lymphocytic (lymphatic, lymphoid) leukemia, FAB L1 or FAB L2. Evidently these two codes, bound to the presence or absence of bone marrow involvement, are in practice a single pathologic entity.

◆ **Precursor B-cell lymphoblastic lymphoma M-9728** (*ICD-9: 200.1; ICD10: C83.4*). It is correlated to code M-9836 (*ICD-9: 204.0; ICD-10: C91.0*) indicating Precursor B-cell lymphoblastic leukemia (Pro-B ALL, Pre-B ALL, ALL-C, etc.). This is the code for the B-cell phenotype; naturally, the same considerations made about the previous code also apply in this case.

◆ **Precursor T-cell lymphoblastic lymphoma M-9729** (*ICD-9: 200.1; ICD-10: C83.4*). This code is correlated to M-9837 (*ICD-9: 204.0; ICD-10: C91.0*), corresponding to Precursor T-cell lymphoblastic leukemia (Pro-T ALL, T-ALL cortical mature, etc.). The same considerations made about the previous code also apply in this case, with the only difference that this code refers to the T-cell phenotype.

It is quite evident that the following codes: M-9727, M-9728, M-9729, together with the corresponding codes indicating bone marrow involvement, M-9835, M-9836, and M-9837, can make up a single pathologic entity, to be kept separate in the case of a statistical report on NH lymphomas.

Lymphoma staging

TNM staging is not suitable for (Hodgkin's and non-Hodgkin's lymphomas: they are therefore grouped in four stages (I through IV) according to Ann Arbor staging (**Table 1**, page 21).² For CLL staging (Chronic lymphocytic leukemia or Small B-cell lymphocytic lymphoma), please refer to the criteria described in the paragraph specifically dealing with this disease (**Table 2 and Table 3**, pages 22-23).³

Explicit and implicit staging

In most lymphoma cases, the clinical data should explicitly give staging at diagnosis, specify whether origin is extra-nodal (E or not E), and they may list, in advanced cases, the organs or extra-nodal sites involved, according to the above-mentioned criteria: this staging should be considered valid by cancer registries. In many cases, however, registries may encounter lymphomas that have not been explicitly staged, but for which the staging is evident and implicit from the clinical documentation: in these cases, which are fairly common in occurrence, registries are allowed to enter the stage, following the above-described criteria, based on the evidence of the data collected at the time of diagnosis. For instance, a case of first finding of LNH in a very advanced stage, with

clear disseminated involvement of lymphatic and extralymphatic organs and general compromise, is a stage IVB, and any involved organs should be specified; a localized and isolated gastric maltoma, instead, is a stage IE, or IAE, and so forth.

Nodal and extranodal lymphomas

Subdivision of lymphomas in nodal and extranodal can be useful for registries for statistical purposes, especially with respect to expected outcomes. For every case of lymphoma the stage at diagnosis should be entered, as described in the previous paragraph.

Cases that are only **nodal** must be recorded with the stage in Roman numerals, without E and without site code, or only with the specific letters marking systemic symptoms (A, B). For instance, a Hodgkin's lymphoma with exclusive nodal locations, in a second stage at diagnosis, with fever and weight loss, should be recorded as IIB.

Whereas **extranodal** cases, which are to be marked with an E, are those in which extranodal locations are present at diagnosis, even if they are mixed with nodal locations (stage II, III and IV). For instance, an isolated maltoma of the stomach should be recorded as IE, or IAE to specify the absence of systemic symptoms.

It must be stressed that lymphomas tend to relapse: Registries can certainly record any recurrences and any new staging, but these, in general, imply the increase in extranodal locations.

A very important aspect with respect to this issue is that not always the sampling site on which the first diagnosis was based is indicative of the stage and complete diffusion of the lymphoma at diagnosis: lymphomas that initially involve only one organ, with or without locations in regional lymph node stations are to be considered extranodal; conversely, nodal lymphomas are lymphomas that involve one or more lymph node stations, whether they involve an organ or more in association with non-local or regional lymph node locations.

Location of a lymphoma in the liver or bone marrow in a patient with nodal lymphoma or extranodal lymphoma of another organ is a sign that the disease has spread: the presence of other locations must therefore be ruled out before accepting a diagnosis of primary lymphoma of the liver or bone.

In case of doubt, or when the clinical record cannot be accessed, registrars must consider the lymphoma to be nodal. If, instead, there is certainty of an extranodal onset, but more than one site is involved, topography code C80.9 should be used. In practice, this means that if a subdivision of lymphomas in nodal and extranodal is attempted based only on the sampling site, doubtful results are reached, with a likely underestimation of extranodal forms – which usually have higher survival – in some registries.

Assigning the sixth digit in the ICD-O code

As is known, a complete ICD-O code has 10 digits. As the first four provide the topographic site, there are six more digits to consider: of these six digits, four refer to the histological type, the fifth digit describes the behavior, which is 3 in all the lymphomas considered here and also in all leukemias (whereas it is 1 in some hematologic immunoproliferative neoplasms); the sixth digit is used to designate immunophenotype (B, T, NK, etc.) in hematologic cancer, whereas in solid tumors grading is inserted here (1, 2, 3, 4, 9).

With the previous ICD-O edition, ICD-O-2, the immunophenotype was 5 for T cells, 6 for B and pre-B cells, 7 for null cells, 8 for NK cells, 9 for undefined. In ICD-O-3 the immunophenotype is implicit in the four-digit morphology code (see above), so the additional sixth digit is no longer required. The only exception is that of code M-9727 and M-9835 (Precursor lymphoblastic lymphoma, NOS and Precursor cell lymphoblastic leukemia, NOS) in which, as a rule, since the leukemia/lymphoma is B- or T-undefined, digit 9 is used. There are also codes of non-definition M-9590, M-9591, and M-9596 in which, of course, the sixth digit will also be 9, as a rule.

Although there is no more need for a sixth digit (tenth of ICD-O), registries can decide to maintain it to identify cases in which diagnosis is supported by immunophenotype characterization.

Bone marrow involvement

Following the most recent findings on hematologic cancer, many correlations between leukemia and lymphoma have been introduced in ICD-O-3: although these correlations have already been described, we consider it useful to list them here again in detail.

These diseases are basically leukemia-lymphomas or leukemized lymphomas, in which the subtle distinction between lymphoma and leukemia only depends on whether there is bone marrow involvement; basically, however, the disease appears to be the same. They are as follows:

- ◆ Small B lymphocytic lymphoma, NOS (M-9670/3) and B-cell CLL (M-9823/3);
- ◆ Burkitt lymphoma, NOS (M-9687/3) and Burkitt cell leukemia (M-9826/3);
- ◆ Precursor lymphoblastic lymphoma, NOS (M-9727/3) and Precursor cell lymphoblastic leukemia, NOS (M-9835/3);
- ◆ Precursor B-cell lymphoblastic lymphoma (M-9728/3) and Precursor B-cell lymphoblastic leukemia (M-9836/3);
- ◆ Precursor T-cell lymphoblastic lymphoma (M-9729/3) and Precursor T-cell lymphoblastic leukemia (M-9837/3).

There is also an explicit correlation, with slightly different pathogenesis, between Malignant lymphoma, lymphoplasmacytic (M- 9671/3) and Waldenström's macroglobulinemia (M-9761/3).

It must be remembered when registering these diseases that, whether they are recorded as lymphoma or as leukemia, they are homogenous pathologic entities, that should be presented jointly in the reports of every registry. Since in practice they are a single cancer, registries must absolutely make sure that they are not recorded as multiple tumors in the same subject. For instance, if a lymphoplasmacytic NH lymphoma is also diagnosed in a case of Waldenström's macroglobulinemia, it is not a second tumor, but only a different aspect of the same neoplastic disease. The same can be said for a case of CLL with a Small B-cell lymphocytic lymphoma.

Chronic lymphocytic leukemia and Small B-cell lymphocytic lymphoma

This sizeable problem in disease classification deserves a separate discussion, especially since this disease is very common, particularly in elderly subjects, and statistically relevant, as the shifting of these cases (from lymphomas to leukemias and vice versa) can have a significant impact on the size of the various traditional subgroups in which registries divide hematologic cancers. In general it is thought that about 30% of leukemias fall into the definition of CLL.

In the nosographic section we have already amply described the nosological correlation between these two conditions, which in most cases are simply two different clinical-hematological presentations of the same neoplastic disease as a consequence of two different diagnostic paths: if the disease is diagnosed by means of blood tests, it will likely be classified as CLL, whereas if it is diagnosed following lymph node involvement and enlargement, after surgical removal of the lymph node, histopathological diagnosis will be of a Small B-cell lymphocytic lymphoma, low grade. Naturally, it is possible, albeit occurring more rarely, that a single subject receives both diagnoses after undergoing both types of diagnostic procedure: in these cases, registries must absolutely avoid considering the case as multiple.

Furthermore, in the field of hematology, pathologists often write in their reports that Small B-cell lymphocytic lymphoma cell is "CLL compatible," in the sense that they indicate to the clinician that their diagnosis is not incompatible with any previous or simultaneous known condition of CLL. This type of report is very helpful for registries, as well, in order to correctly register these cases.

Classification of Chronic lymphocytic leukemia

Having said that these two conditions are almost always practically the same thing, or rather, two different nosographic terms used to define the same neoplastic disease, it must be added that in clinical hematology Chronic lymphocytic leukemia cases are not all simply hematologic aspects of a lymphocytic B-cell NHL: 95% of cases of CLL originates from B lymphocytes, but in the remaining 5% leukemic proliferation involves T lymphocytes. Furthermore, even within the series of B lymphocyte diseases, there are a few fairly rare conditions, other than Small B-cell lymphocytic lymphoma, that cause CLL, as shown in

Table 2. A logical conclusion can be easily drawn after perusing this table, i.e., although there is a clinical-hematological heterogeneity of what is defined as CLL, the new ICD-O-3 code almost totally cancels it, because it assigns a different code, separate from that of CLL, to most hematological pathologic entities responsible for said heterogeneity. On the other hand, code M-9823/3 (used for both B-cell CLL and CLL, NOS) is the only possible code that may be used to T-cell forms of CLL, which are very rare; however, since B-cell forms are largely prevalent (98%), M-9823 CLLs will be considered B-cell unless the sixth digit “5” is specified in the morphology code.

CHRONIC LYMPHOCYTIC LEUKEMIA: CURRENTLY USED DIAGNOSTIC CRITERIA

Major hematological criteria

- ❖ sustained lymphocytosis: $>10,000$ WBC, but usually between 20,000 and 100,000 /mm³ and absolute lymphocyte count at least $>4,000$ but, more often, from 5000-10,000 upwards; lymphocytes often account for 70-90% of total leukocytes
- ❖ peripheral blood smear with hematological diagnosis of CLL (and possible presence of smudge cells)
- ❖ bone marrow smear with lymphoid metaplasia above 30-50%
- ❖ immunophenotype and immunohistochemistry positive for CLL (generally of the B type, much more rarely of the T type)

Minor hematological criteria

- ❖ anemia, thrombocytopenia, hypogammaglobulinemia, paraproteinemia, etc.

Clinical features

- ❖ in at least 30% of cases the disease is asymptomatic and is incidentally discovered during routine examinations
- ❖ general signs in 70% of cases: fatigue, weight loss, fever, general itching
- ❖ enlarged lymph nodes, in as many as 50% of cases, usually moderate (it is on these lymph nodes, if they are removed, that Small B-cell NH lymphoma diagnoses are made, see above)
- ❖ enlarged spleen: 30% of cases
- ❖ enlarged liver: 20% of cases
- ❖ infiltration of B-cells in various internal organs, with consequent thickening and enlargement, which are sometimes visible on x-ray: besides the liver and spleen, organs thus affected may include the kidneys, lungs, intestine, retro-orbital tissues, parotid and salivary glands, etc.

Chromosomal abnormalities

- ❖ in B-CLL trisomy 12 and structural abnormalities of chromosome 6 are frequently observed
- ❖ in T-CLL structural abnormalities of chromosome 7q are found

Complications in the clinical course of CLL (which is often quite long)

- ❖ intercurrent infections
- ❖ autoimmune hemolytic anemia or thrombocytopenia
- ❖ appearance of secondary neoplasms (very important for cancer registries)

Diagnostic criteria for Chronic lymphocytic leukemia

Very often, registrars do not find histopathological data explicitly referring to a CLL case in anatomical pathology databases (the reason is apparent after the above explanations). Pathological diagnosis is only

present on lymph node (as a rule surgically removed nodes) or bone marrow biopsy reports: in these cases the diagnosis is of Small B-cell NH lymphoma (and various synonyms thereof), in some cases with explicit mention of compatibility with CLL. This is

the major histopathological confirmation of CLL diagnosis.

Much more frequently, however, registrars will find no histopathological documentation because CLL diagnosis is clinical-hematological and is very often made at the physician's office or as an outpatient procedure, and only much more rarely during hospitalization. Diagnosis is mostly suspected after routine examinations and confirmed with hematological procedures such as peripheral blood or bone marrow smears, or other types of procedures (immunohistochemistry, immunophenotype, etc.) performed in hematological labs. As a consequence, registrars often find themselves reviewing clinical documentation on this disease. The inset on this page lists the hematological diagnostic criteria used for CLL.⁴

Conversely, diagnosis of Small B-cell lymphocytic lymphoma shall be made in the following cases:

- ◆ absolute lymphocyte count under 5,000/ mm³ in peripheral blood;
- ◆ evidence of localized disease in one or few lymph nodes (enlarged lymph nodes in a single region or few regions, highly asymmetrical) or in single extranodal anatomic sites (e.g., orbit, lung);
- ◆ histology report of lymphoma (Small B-cell lymphoma);
- ◆ bone marrow biopsy with lymphocyte infiltration below 30%.

Staging of chronic lymphocytic leukemia

Considering the particular aspects outlined above, it is evident that traditional staging of lymphomas is ill suited to CLL. Two other clinical staging criteria are therefore used for CLL (Table 3).⁵⁻⁷

Lymphoma or leukemia? Which site? Criteria for case management of this disease

From all the above it is evident that, apart the rare case of CLL-T, CLL and Small B-cell lymphocytic lymphoma are simply the same disease, which arises with two different presentations of site: in the blood and bone marrow as CLL; in lymph nodes, lymphatic or extralymphatic organs as B-cell lymphoma. Therefore only the site establishes whether the disease is leukemia or lymphoma. Currently in most registries this hematological neoplasm is therefore divided into two different classifications: as leukemia (site C42.1) under 204.1 in ICD-9 (C91.1 in ICD-10) and as lymphoma (site C77.0-9, in most cases) under 200.1 (or 202) in ICD-9 (C83.0 in ICD-10).

Partly to make correct analysis of incidence and survival data possible, it is recommended to maintain the current registration and coding methods, whereas when analyzing incidence and survival (as well as trends), we advise the following procedures:

- ◆ analyze NHLs separating Small B-cell lymphocytic lymphomas based on morphology;
- ◆ carrying out the analysis unifying in a single category Small B-cell lymphocytic lymphomas and B-CLLs; this category would thus become a very homogeneous group (apart from the rare case of T-CLL).

This operation would also have the advantage of reducing the significant clinical and prognostic diversity of the large NH lymphoma group. It must be underlined NHLs include high-, medium-, and low-grade malignant lymphomas, adult and childhood lymphomas, B-cell and T-cell lymphomas, lymphomas that require simple outpatient treatment and aggressive lymphomas that require heavy CT therapies, bone marrow transplant, etc.; thus removing a fairly large portion from the NHL set reduces a part of its inhomogeneity. It must be borne in mind, incidentally, that mortality for this disease is relatively low, since it is a low grade disease: only cases in III or IV Rai stage or C Binet stage may have a poor prognosis. Very often, CLL carriers die from other diseases.

However, both ICD-9 and ICD-10 maintain the ambiguity between the two diseases, with two distinct codes: 204.1 and 200.1 in ICD-9, C91.1 and C83.0 in ICD-10, respectively. The same dichotomy is thus also encountered in mortality analysis, and in this case, too, the recommended procedure is that described above, although generally the diagnosis of death is more generic (Lymphoma or NHL). Obviously, this equivalence must be also taken into account when tracing back DCI cases.

Inpatient and outpatient data in CLL (prevalence and data loss in a cancer registry)

Chronic lymphocytic leukemia (or Small B-cell lymphocytic lymphoma) is typically a slow-growing disease, which is often diagnosed and followed-up outside a hospital setting even for several years. As mentioned above with respect to clinical parameters, CLL can be asymptomatic and found incidentally through blood tests, or it can be symptomatic and found as a result of intercurrent infections. This type of disease is therefore difficult to handle for registries, since its clinical course and features are ill suited to a normal registration. We therefore advise registries, as far as possible, to treat these cases manually, i.e., to review the clinical documentation (if possible outpatient documentation, as well), and especially the clinical history of cases, to establish the exact onset of the disease in question. This aspect will be discussed further on, when discussing diagnosis and incidence of outpatient cases. Suffice it however to say that hospital admissions that have CLL codes in the HDDs very

often do not correspond to the true ascertained beginning of the condition, since they are initially prompted by the onset of complications, intercurrent diseases, specific therapies, etc., in subjects that sometimes have been known and followed outside a hospital setting for years. The same can be said about histopathological diagnoses, which often do not indicate the ascertained onset of the disease, but are made during follow-up over the disease's long clinical course.

As an overall result, cases of CLL in registries are altered, almost as a rule, by the erroneous entering of prevalent cases that are considered incident. On the other hand, since this disease is typically managed in an outpatient setting and histopathological diagnosis for this disease is available only in a small number of cases, CLL cases cannot all be found in the common databases (HDD and anatomical pathology reports) used by the registries: this means that a certain number of cases is inevitably lost. The loss of CLL cases is, generally, slightly higher than the number of prevalent cases erroneously entered. The only way to avoid these technical difficulties is to partner with hematological clinics or centers that periodically follow these cases.

Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (or disease)

Between these two entities, respectively defined by code M-9671/3 and M-9761/3 of ICD-O-3, there is a clinical-pathological correlation that is very similar to that discussed in the previous paragraph; however, and this is no minor difference, this disease is much rarer than CLL. It is a small B-cell neoplasm (or plasmacytic/plasmacytoid lymphoma) which normally involves the bone marrow, lymph nodes, and spleen, with the presence of a monoclonal serum protein and accompanied in many cases by hyperviscosity or cryoglobulinemia.⁸

First of all, it is essential that registries avoid registering these cases as multiple (lymphoplasmacytic lymphoma + Waldenström's disease). Second, it must be noted that Waldenström's macroglobulinemia is still coded today in ICD-9 CM as 273.3, therefore outside the usual 140-208 range of malignant neoplasm codes (as all myelodysplastic syndromes): to trace it in HDDs, registries must therefore carry out a specific search, taking into consideration an extended range of HDD codes. Waldenström's macroglobulinemia is assigned a true malignant neoplasm code only by ICD-10 (C88.0). Its mandatory site code is the blood (C42.0).

Furthermore, it must be added that all cases of IgM monoclonal gammopathy are true Waldenström's diseases: just as Multiple myeloma, with which it has a certain etiological similarity, Waldenström's disease also has similar “satellite” conditions that are “benign” or “of

uncertain behavior”, which are not considered true Waldenström's diseases; they are the following: Benign monoclonal gammopathy (or IgM MGUS) and secondary (or accompanying) macroglobulinemias. The latter are frequently associated with other solid tumors, hematologic neoplasms (lymphomas, CLL) and non-neoplastic diseases (collagen diseases, chronic infections, HCV hepatopathy, polyneuropathy, etc.): registries should not take these secondary conditions into account; only in the case of explicit diagnosis of IgM MGUS, they may be included in ICD-O-3 code M-9765/1 and as such recorded in the registry: in any case they do not fall into the category of malignant neoplasms.

Waldenström's macroglobulinemia therefore is not merely an IgM monoclonal gammopathy, but an entire clinical condition comprising the following: increase in serum viscosity (fatigue, general malaise, migraines, blurring or loss of vision, Raynaud's phenomenon, “paraproteinemic” coma), anemia and hemorrhagic diathesis (tendency to bleed from the mucosa, also melena, hematuria, metrorrhagia, etc.), enlarged liver and spleen and/or localized or diffuse lymphadenopathy and, rarely (10% of cases), presence of a severe sensory, symmetric demyelinating neuropathy, mainly to the lower appendages, due to the presence of anti-myelin associated antibodies (anti-MAG, Myelin Associated Glycoprotein).

Diagnostic criteria and coding

Waldenström's macroglobulinemia is diagnosed in the presence of the following:

- ◆ any extent of IgM monoclonal gammopathy, associated to lymphoplasmacytic infiltrate in the bone marrow (flow cytometry, immunohistochemistry) (Athens 2002 Workshop⁹);

or:

- ◆ IgM monoclonal gammopathy >1 g/dL with no histological confirmation in person of age ≥50 years (ENCR 1999¹⁰).

It is coded as follows:

- ◆ **MGUS IGM**, when a monoclonal gammopathy is present (without bone marrow infiltration if under 50 years of age, if <1 g/dL from 50 years up);
- ◆ **lymphoplasmacytic lymphoma**, when the monoclonal gammopathy is associated with limited or diffuse nodal or extranodal locations, without bone marrow infiltration, or when the monoclonal component is missing or appears later.

Therefore, as in the previously discussed case of CLL/B-cell lymphocytic lymphoma, we advise registries to keep the correlated diseases separate, in the corresponding sites: mandatorily blood (C42.0) for Waldenström's disease, or lymph node/s or parenchymal organs for plasmacytic lymphoma, giving precedence to the lymphatic site when both codes are present. Part of the reason behind this

suggestion is that, as in the case of CLL-B-cell lymphocytic lymphoma, these two correlated diseases also remain divided in mortality, since both ICD-9 CM and ICD-10 do not unify them, and they may therefore be coded differently in the death certificate. We suggest, instead, that registries unify the two codes under M-9761/3 for publications, analyses, data presentations, and so forth.

Hodgkin's and non-Hodgkin's lymphoma

See section on multiple hematologic neoplasms.

Other lymphomas – miscellaneous

- ◆ **Mediterranean lymphoma:** see immunoproliferative disorders, code M-9764/3.
- ◆ **HIV-correlated lymphomas:** 80-90% of these are highly malignant, with either B phenotype, or non B-non T phenotype(9714/3); they are almost always extranodal. The most frequent locations are the following: CNS (31%), liver (26%), gastrointestinal tract (24%), bone marrow; (24%), spleen (21%), lung (7%), skin (7%), pancreas (5%), etc.
- ◆ **Castleman's disease (angiofollicular lymphoid hyperplasia):** although it can be a serious lymphatic disease, it is neither a lymphatic neoplasm (neither malignant nor benign), but since it is sometimes called Castleman's lymphoma, it can give rise to doubts in registries. It must not be collected nor registered, except in NSE cases in which there might be a possible differential diagnosis with lympho-hematological malignancies.

Plasma cell, mast cell, and histiocytic neoplasms, and immunoproliferative disorders

Multiple myeloma, smoldering myeloma and MGUS

Plasma cell tumors (plasmacytomas) take up codes M-9731 to M-9734, but they also have close links with immunoproliferative disorders, listed from M-9760 to M-9769.

Multiple myeloma (M-9732/3; ICD-9: 203.0; ICD-10: C90.0) is a malignant tumor of the B lineage, characterized by uncontrolled proliferation of bone marrow plasma cells. since these cells normally produce antibody immunoglobulins, multiple myeloma can also be recognized by the presence of monoclonal immunoglobulins or fragments of the same in the serum and/or urine. From a diagnostic point of view, a myeloma is generally diagnosed based on the following elements:

- ◆ finding of a high, homogeneous quantity of monoclonal immunoglobulins (protein M – IgG, IgA, rarely IgD or IgE) or of their fragments in the serum and/or urine (κ or λ “light chains”, responsible for Bence-Jones proteinuria), through

electrophoresis, immunoelectrophoresis, etc. (about 30% of myelomas are asymptomatic at diagnosis);

- ◆ plasma cell infiltration in the bone marrow and/or other tissues (histological diagnosis);
- ◆ osteolytic bone locations, usually accompanied by bone pain and/or pathologic fractures (about 35% of cases present with bone pain at onset): bone locations are most common in the vertebral column, pelvis, ribs, and cranium;
- ◆ presence of secondary anemia (in about 20% of cases), due to uncontrolled plasma cell invasion of the bone marrow;
- ◆ kidney failure or hypercalcemia (in about 15% of cases): kidney failure, hypercalcemia, and intercurrent infections (do to diminished immune response) are among the most common complications also in the clinical course of myeloma (myelomatous kidney, hypercalcemia syndromes).

It must also be added that myelomatous diseases have a slow, indolent course; they are often discovered incidentally, not always within a hospital setting, and are then followed over time in an outpatient setting. At times they are preceded, even years before, by the diagnosis of an isolated monoclonal gammopathy, but without an actual diagnosis of multiple myeloma. This extremely common situation is defined as monoclonal gammopathy of undetermined significance, or MGUS, which can be coded M-9765/1, and is obviously not to be placed with malignant tumors. There are therefore precise diagnostic criteria to distinguish MGUS from true Multiple myeloma. These criteria are quite important for registries because they make it possible, with subtle precision, to distinguish behavior /1 from behavior /3.

Sometimes it is difficult to distinguish between MGUS and forms of Smoldering myeloma, which can remain asymptomatic even for years, albeit in the absence of specific treatment. Smoldering myeloma (SMM) is generally not advanced, it falls into the diagnostic criteria listed above, but remains asymptomatic without evolving for even long periods of time. Since it falls into the diagnostic criteria of Multiple myeloma, Smoldering myeloma is not a MGUS and as a rule should be recorded with /3.

In the differential diagnosis^{11,12} shown in **Table 4 a/b** (page 24) other parameters are also used, such as the labeling index and interleukin 6 doses (IL-6). The following are particular situations that may be encountered by registrars:

- ◆ **Non-secretory myeloma** (about 1% of cases), in which no circulating monoclonal component can be identified, but bone marrow plasmacytosis and bone lesions are present;

- ◆ **Micromolecular myeloma (mm)**, more frequent, in which no myelomatous serum proteins are observed, but only free light chains, in the serum and urine (about 10-20% of myelomas).

Considering the clinical and hematologic peculiarities of myeloma, staging is performed using the criteria¹²⁻¹³ listed in **Table 5** (page 25). It must be borne in mind that the 1999 ENCR rules on basis of diagnosis allow for morphology coding of myeloma even in the presence only of serum or urine data that fall into the range of the above-mentioned “major criteria”, providing the subject is at least 40 years of age. Finally, it must be stressed that monoclonal components can also be found in other diseases (non-Hodgkin's lymphomas, chronic lymphocytic leukemia, cryoglobulinemia, Sjögren's syndrome, sarcoidosis, hepatic cirrhosis, and, rarely, other neoplasms such as breast, colon, and prostate cancer); this must be ruled out before diagnosing MGUS. A special case is that of amyloidosis, which is characterized by deposit of amyloid protein in the tissues, with a monoclonal component in the serum and/or urine: the source of amyloid proteins is a population of monoclonal plasma cells in the bone marrow, so it is necessary to follow the patient to make sure that the final diagnosis is not that of Multiple myeloma with amyloidosis.

Other plasmacytomas

Plasmacytomas can also, more rarely, present in localized, single forms, called “solitary,” both in the bone marrow itself or in the bones, and in completely extramedullary sites. As a rule, these solitary plasmacytomas are surgically removed or undergo radiation therapy and sometimes are also found incidentally during the removal of masses, cysts, etc.; it is known, however, that those occurring in the bone or bone marrow progress within 5-10 years into true multiple myelomas in 60-70% of cases, while in extramedullary ones, subsequent appearance of myeloma only occurs in 20-25% of cases. Obviously, if a solitary plasmacytoma progresses into a true multiple myeloma, the pathologic sequence (which may take years) should not lead registries to consider the case as multiple, but rather as a single neoplastic process, that is incident on the date of the diagnosis of solitary plasmacytoma and subsequently progressed into multiple myeloma.

A diagnosis of **solitary plasmacytoma of the bone** or soft tissue requires proof of a true extramedullary lesion, with less than 5% of plasma cells in the bone marrow and biopsy confirmation of the myelomatous nature of the lesions by CT- or MRI-guided needle biopsy.

These plasmacytomas are coded as follows:

- ◆ **Solitary plasmacytoma of bone M-9731/3** (*ICD-9: 238.6 or 203.8, depending on registrars; ICD-10 C90.2*);

- ◆ **Extramedullary plasmacytoma M-9734/3** (*ICD-9 and ICD-10, same as above*)

In more than 80% of cases it is localized in the nasopharynx (rarer sites are pleuropulmonary, nodal, intestinal, or CNS);

- ◆ **Plasma cell leukemia M-9733/3** (*ICD-9: 203.1; ICD-10: C90.1*)

A rare disease, which we mentioned when discussing CLL, as it can be classed as one of its clinical-morphological variants.

Other immunoproliferative disorders

These are generally rare satellite diseases of plasmacytomas; not all of them are considered to have behavior /3, because often they are /1.

- ◆ **Myeloproliferative disease, NOS M-9760/3** (*ICD-9: 203.8; ICD-10: C88.9*)

A non-specific code.

- ◆ **Heavy chain diseases M-9762/3** (*ICD-9: 273.2; ICD-10: C88.1-C88.2*)

These extremely rare diseases are malignant lymphoplasmacytic tumors that synthesize and secrete heavy chain immunoglobulins. This code includes at least three clinically different conditions, that produce three types of heavy chains:

- ◆ α heavy chain disease, or Seligmann's disease;
- ◆ γ heavy chain disease, or Franklin's disease;
- ◆ μ heavy chain disease.

- ◆ **Mediterranean lymphoma or Immunoproliferative small intestinal disease M-9764/3** (*ICD-9: 203.8; ICD-10: C88.3*)

Generally localized in the small intestine (C17), it is an intestinal lymphoproliferative disease, most common in the Mediterranean region and the Middle-East. In about half the cases a marker, the shortened form of the α heavy chain is identified. Positive cases are defined as IPSID (ImmunoProliferative Small Intestinal Disease), the rest as non-IPSID. The two forms also have different clinical presentation. The other codes in this group all fall into behavior /1, i.e., just as happens with MGUS, they cannot be considered true malignant neoplasms.

- ◆ **Angiocentric immunoproliferative lesion or Lymphomatoid granulomatosis M-9766/1** (*ICD-9: 238.7; ICD-10: D47.7*)

Probably correlated to the evolution of NK/T-cell lymphoma.

- ◆ **Angioimmunoblastic lymphadenopathy (AIL) M-9767/1** (*ICD-9: 238.7; ICD-10: D47.7*).

- ◆ **T-gamma lymphoproliferative disease M-9768/1** (*ICD-9: 238.7; ICD-10: D47.7*).

- ◆ **Immunoglobulin deposition disease** (e.g., systemic light chain disease and primary amyloidosis) **M-9769/1** (*ICD-9: 277.3; ICD-10: E85.9*).

Here, amyloidosis must be **primary**. Amyloidosis is often secondary, for instance to multiple myeloma, and in that case it should not be taken into account by registries: incidence, basis of diagnosis, stage, etc. are in that case those relevant to the myeloma.

Mast cell and histiocytic tumors

Mast cell neoplasms are very rare. Mastocytoma, NOS has code M-9740/1 (*ICD-9: 238.5; ICD-10: D47.0*). All other mast cell diseases have malignant behavior.

- ◆ **Malignant mastocytoma, or Mast cell sarcoma M- 9740/3** (*ICD-9: 202.6; ICD-10 C96.2*).
- ◆ **Malignant mastocytosis M-9741/3** (*ICD-9: 202.6; ICD- 10: C96.2*).
- ◆ **Mast cell leukemia** (in site C42.1) M-9742/3 (*ICD- 9: 207.8; ICD-10: C94.3*).

Histiocytic neoplasms prevalently affect children or youths; they fall partly under behavior /3, and partly under /1.

- ◆ **Malignant histiocytosis, or Malignant reticuloendotheliosis and Malignant reticulosis M-9750/3** (*ICD-9: 202.3; ICD- 10: C96.1*).
- ◆ **Letterer-Siwe disease, or Langerhans cell histiocytosis, disseminated M-9754/3** (*ICD-9: 202.5; ICD-10: C96.0*).

Also known as Acute progressive histiocytosis X and Non-lipid reticuloendotheliosis.

- ◆ **Histiocytic sarcoma, or True histiocytic lymphoma M- 9755/3** (*ICD-9: 200.0; ICD-10: C96.3*).
- ◆ **Langerhans cell sarcoma, Interdigitating dendritic cell sarcoma, Follicular dendritic cell sarcoma**, respectively **M-9756/3, M- 9757/3, M-9758/3** (*ICD-9: 202.3; ICD-10: C96.7*).

The other pathologic entities related to Langerhans cell histiocytosis (all with *ICD-9 code CM 277.8* and *ICD-10 code D76.0*) have behavior /1.

- ◆ **Langerhans cell histiocytosis (or granulomatosis), NOS M-9751/1**: also known as Histiocytosis X, NOS.
- ◆ **Langerhans cell histiocytosis (or granulomatosis), unifocal (or monostotic), or Eosinophilic granuloma M-9752/1**.
- ◆ **Langerhans cell histiocytosis, multifocal (or polyostotic)**, also known as Hand-Schüller-Christian disease, M-9753/1.

Leukemia

Innovations of ICD-O-3

ICD-O-3 significantly reorganized the classification of leukemias, with changes in codes, disappearance of old codes or introduction of new codes, as well as changes in entire groupings.

- ◆ *Eliminated groupings*. No less than six *leukemia* groupings were eliminated, by aggregating myeloid leukemias, shifts to other groupings, etc. In practice,

only the following four groupings are left: NOS, lymphoid, myeloid and other leukemias.

- ◆ *Introduction of new codes based on cytogenetic abnormalities (especially in acute myeloid leukemia)*.¹⁴ It is very important for registries to consider that when these abnormalities are included in the hematological diagnosis, they take precedence in the classification of the case compared to other data, such as FAB type.
- ◆ *Introduction of new codes for "secondary" leukemias* . They are specific codes for forms associated with myelodysplasia (AML with multilineage dysplasia), or for therapy-related leukemias (alkilating agents, epipodophylotoxin).
- ◆ *Erythroleukemia and Acute erythremia*. Considered AML type M6 (FAB M6). Chronic erythremia is now known as Polycythemia vera.
- ◆ *Lymphosarcoma cell leukemia*. It is classified as Lymphocytic leukemia, NOS.
- ◆ *Chronic myelomonocytic leukemia*. Is still grouped with "other" leukemias.
- ◆ *Monocytic leukemia*. Grouped with Myeloid leukemia (except for chronic myelomonocytic leukemia).
- ◆ *Basophilic, eosinophilic, megakaryoblastic leukemia and myeloid sarcoma*. The are classified as myeloid leukemia.
- ◆ *Acute panmyelosis and Acute myelofibrosis* . They have been joined and grouped with myeloid leukemia.
- ◆ *Plasma cell leukemia*. It has been moved with plasma cell tumors.
- ◆ *Chronic eosinophilic and chronic neutrophilic leukemia*. These new definitions are grouped with chronic myeloproliferative disorders.

FAB type

The FAB (French-American-British) system¹⁵ is a classification of lymphoid and myeloid leukemia based on the microscopic appearance of cells after routine staining (**Table 6**, page 26): it provides a good classification of leukemia based on morphology and cytochemistry. It has been used for approximately 30 years and it is an internationally accepted system. In the past few years, new immunology, cytogenetic, and molecular biology techniques have made it possible to integrate and improve the FAB system with the introduction of the MIC classification (Morphology, Immunology, Cytogenetics, Working Formulation). MIC thus completes and improves FAB. Therefore, when a precise hematological diagnosis is available, leukemia correlated to specific cytogenetic abnormalities must be recorded using specific codes, using the FAB classification only when it is the only information available.

Disease classifications

Leukemias fall within code range M-9800 and M-9948 of ICD-O-3. All codes are in behavior /3 (with site C42.1). They are divided into four main groups.

◆ Leukemia, NOS

- ◆ **Leukemia, NOS** M-9800/3 (*ICD-9: 208.9; ICD-10: C95.9*).
- ◆ **Acute leukemia, NOS** M-9801/3 (*ICD-9: 208.0; ICD-10: C95.0*).
- ◆ **Acute biphenotypic leukemia or bilineage or of ambiguous lineage** M-9805/3 (*ICD-9: 208.8; ICD-10: C95.7*)

They are leukemias with mixed lymphoid and myeloid phenotypes (polyphenotypic); 15-25% of ALLs express antigens specific to the myeloid series, and, vice versa, lymphoid antigen expressions are often found in AMLs: 15-20% of acute leukemias are estimated to fall into this category.

◆ Lymphoid leukemias

- ◆ **Lymphoid (or lymphatic or lymphocytic) leukemia, NOS** M-9820/3 (*ICD-9: 204.9; ICD-10: C91.9*). Includes subacute lymphoid leukemia, aleukemic lymphatic leukemia and lymphosarcoma cell leukemia.
- ◆ **Chronic lymphocytic leukemia M-9823/3**. It is the CLL described previously in the chapter on Lymphomas.
- ◆ **Burkitt cell leukemia M-9826/3** It is FAB L3, described previously in the chapter on Lymphomas with Burkitt lymphoma M-9687/3.
- ◆ **Adult T-cell leukemia/lymphoma (HTLV- 1 positive) or Adult T-cell lymphoma/leukemia M-9827** (*ICD-9: 204.8; ICD-10: C91.5*)
An HIV-1 correlated T-cell neoplasm.
- ◆ **T-cell (or NK cell) large granular lymphocytic leukemia or T cell large granular lymphocytosis M-9831** (*ICD-9: 204.8; ICD-10: C91.7*)
Also known as chronic LGL leukemia.
- ◆ **Prolymphocytic leukemia, NOS M-9832/3, B-cell type M-9833/3, T-cell type M-9834/3** (*ICD-9 204.8; ICD-10 C91.3*).¹⁶
- ◆ **Precursor lymphoblastic leukemia, NOS** M-9835/3, **B-cell type M-9836/3, T-cell type M-9837/3: (FAB L1, FAB L2)**
Previously described in the chapter on Lymphomas, codes M-9727, M-9728 and M-9729.

◆ Myeloid leukemias

- ◆ **Acute myeloid leukemia, type M6 or FAB M6, or acute erythroid leukemia, or**

erythroleukemia, erythremic myelosis, acute erythremia (or Di Guglielmo's syndrome) M-9840/3 (*ICD-9: 207.0; ICD-10: C94.0*)

Rare (2%) as primary AML, but more common (20%) among leukemias secondary to chemotherapy.

- ◆ **Myeloid leukemia (or granulocytic, or myelogenous, or myelocytic, or myelomonocytic, or nonlymphocytic leukemia), NOS, or subacute myeloid leukemia, or aleukemic myeloid leukemia M-9860/3** (*ICD-9: 205.8, 205.9, 205.2, 206.8, 206.9, 206.2, 206.1; ICD-10: C92.7, C92.9, C92.2, C93.7, C93.9, C93.2, C93.1*)
Also known as Eosinophilic leukemia, monocytic, NOS, Subacute monocytic leukemia, Chronic subacute leukemia, and Aleukemic monocytic leukemia.
- ◆ **Acute myeloid leukemia (or acute granulocytic, or myelogenous, or myelocytic, or nonlymphocytic leukemia), NOS M-9861/3** (*ICD-9: 205.0; ICD-10: C92.0*)
For cases without type (FAB or other). This code is also correlated to subsequent code M-9930/3 (*ICD-9: 205.3; ICD-10: C92.3*) for Myeloid or granulocytic sarcoma, or Chloroma, with which it could constitute a single pathologic entity.
- ◆ **Chronic myeloid leukemia (or granulocytic, or myelogenous or myelocytic) , NOS M-9863/3** (*ICD-9: 205.1; ICD-10: C92.1*)
With no further cytogenetic definitions.
- ◆ **Acute promyelocytic leukemia, t(15;17)(q22;q11-12), or PML/RAR-alpha, FAB M3 M-9866/3** (*ICD-9: 205.0; ICD-10: C92.4*)
It accounts for about 5-10% of AMLs and is a typical example of a code that is nowadays validated by typical cytogenetic abnormalities.
- ◆ **Acute myelomonocytic leukemia, FAB M4 M-9867/3** (*ICD-9: 205.0; ICD-10: C92.5*)
Represents about 20-30% of AMLs.
- ◆ **Acute basophilic leukemia M-9870/3** (*ICD-9: 205.0; ICD-10: C92.7*).
- ◆ **Acute myeloid leukemia with abnormal eosinophils, t(16;16)(p13;q11), or CBF-beta/MYH11, FAB M4Eo M-9871/3** (*ICD-9: 205.0; ICD-10: C92.5*)
Another typical example of acute leukemia validated by cytogenetic abnormalities.
- ◆ **Acute myeloid leukemia, with minimal differentiation, or acute myeloblastic leukemia, known as "FAB M0" M-9872/3** (*ICD-9: CM 205.00-01; ICD-10: C92.0*).

- ◆ **Acute myeloid leukemia without maturation, FAB M1 M-9873/3** (*ICD-9: 205.0; ICD-10: C92.0*)
Represents about 15-20% of AMLs.
- ◆ **Acute myeloid leukemia with maturation, FAB M2, NOS M-9874/3** (*ICD-9: 205.0; ICD-10: C92.0*)
Represents about 10-15% of AMLs.
- ◆ **Chronic myeloid leukemia, BCR/ABL positive, or CML Ph chromosome (Phi1) positive, or t(9;22)(q34;q11) M-9875/3** (*ICD-9: CM 205.10-11; ICD-10: C92.1*).
- ◆ **Atypical chronic myeloid leukemia, BCR/ABL negative, or atypical CML, Ph chromosome (Phi1) negative M-9876/3** (*ICD-9: 205.1; ICD-10: C92.1*).
- ◆ **Acute monocytic or monoblastic leukemia, FAB M5 M-9891/3** (*ICD-9: 206.0; ICD-10: C93.0*)
About 2-5% of AMLs.
- ◆ **Acute myeloid leukemia with multilineage dysplasia or leukemia with (or without) previous myelodysplastic syndrome M-9895/3** (*ICD-9: 205.0; ICD-10: C92.0*)
An example of AML secondary to myelodysplasia (this is the code which should be used when a myelodysplasia had previously been found, which with the new ICD-O-3 classifications becomes the case that enters into incidence).
- ◆ **Acute myeloid leukemia, t(8;21)(q22;q22), or AML1(CB-alpha)/ETO, FAB M2 M-9896/3** (*ICD-9: 205.1; ICD-10: C92.0*)
A variant, with cytogenetic abnormality, of M-9874/3 (see above); it accounts for about 10-15% of cases of AML.
- ◆ **Acute myeloid leukemia, with 11q23 abnormalities, or acute myeloid leukemia, MLL M-9897/3** (*ICD-9: 205.0; ICD-10: C92.0*).
- ◆ **Acute megakaryoblastic leukemia, FAB M7 M-9910/3** (*ICD-9: 207.2; ICD-10: C94.2*)
It accounts for less than 1% of primary AMLs, but it seems to represent 20-50% of leukemias secondary to myelodysplasia.
- ◆ **Therapy-related acute myeloid leukemia, NOS (alkilating agents, epipodophylotoxin) M-9920/3** (*ICD-9: 205.0; ICD-10: C92.0*)
This code should preferably be used in an acute myeloid leukemia recorded as being secondary to chemotherapy.
- ◆ **Myeloid or Granulocytic sarcoma, or Chloroma M-9931/3** (*See above, code 9861*).
- ◆ **Acute panmyelosis with myelofibrosis, or acute myelofibrosis, or acute (malignant) myelosclerosis M-9931/3** (*ICD-9: 207.8; ICD-10: C94.4, C94.5*).
- ◆ **Other leukemias**
 - ◆ **Hairy cell leukemia or leukemic reticuloendotheliosis M-9940/3** (*ICD-9: 202.4; ICD-10: C91.4*)
It accounts for about 2% of adult leukemias.
 - ◆ **Chronic myelomonocytic leukemia, NOS, type I, type II, in transformation (CMML) M-9945/3** (*ICD-9: CM 205.80-81; ICD-10: C92.7*)
This disease is also often classified among myelodysplastic syndromes (MDSs) and is defined by absolute monocytosis with myeloid <5% in peripheral blood, while myelomonocytic blasts in the bone marrow should be between 5 and 20%.
 - ◆ **Juvenile (chronic) myelomonocytic leukemia, JMML M-9946/3** (*ICD-9: 205.8; ICD-10: C92.7*)
Often classified among MDSs.
 - ◆ **Aggressive NK cell leukemia M-9948/3** (*ICD-9: 207.8; ICD-10: C94.7*).

Acute and chronic leukemias: incidence and registration problems

Leukemia courses vary greatly due to their polymorphous clinical aspect, and this has significant impact on their registration. Let us mention a few difficulties in registration.

- ◆ In most cases no diagnoses are found in anatomical pathology databases because diagnosis, histotype, cytogenetics, etc., are performed in hematological labs. The date of incidence should be that of the first positive test for leukemia: peripheral blood or bone marrow smears are considered equivalent to normal cytology. According to current IARC guidelines, even a positive cytochemistry, cytogenetic, etc., examination can be used as basis of incidence if it is specific to the disease in question: therefore, if a blood test with positive cytogenic analysis was performed before cytohematological diagnosis of leukemia, the date of the blood test must be used as the incidence date for the case. In general, however, the first diagnosis is based on a blood or bone marrow smear. In the absence of data from a hematologic lab, the date of first hospital admission for acute leukemia found in the HDD shall be considered (very often, it is almost the same date as that of cytohematological testing). Whereas clinical diagnosis of acute leukemia is almost

always found in HDDs, the same does not occur for chronic leukemia cases.

- ◆ As previously mentioned with respect to CLL-small B-cell lymphocytic lymphoma, in chronic leukemias the first diagnosis, first course therapy and its follow-up generally take place in an outpatient setting. For registries this implies a number of problems in defining both date of incidence and exact basis of diagnosis: these problems can often only be solved manually, acquiring the entire clinical history of the case and reviewing all pertinent clinical documentation.
- ◆ It is in any case frequent in these situations for registries to consider incident cases that are actually prevalent (and in some cases have been so for years); on the other hand, the fact that many of these cases are managed in an outpatient setting inevitably results in the loss of some of them, which registries will never learn of. These problems may be solved only by a close cooperation between registries and physician's offices, outpatient clinics, etc. that follow these cases.

It must be borne in mind, finally, that based on the 1999 ENCR rules, it is possible to diagnose Leukemia, NOS (M-9800/3) even without histocytological basis, solely by clinical diagnosis.

Chronic myeloproliferative and myelodysplastic disorders

Innovations of ICD-O-3

This group of hematologic neoplastic diseases underwent considerable changes with the third edition of the ICD-O.

- ◆ *Passage to behavior /3*. A very significant number of hematological diseases was changed from /1 to /3: Polycythemia vera, Myelofibrosis (or Myelo-sclerosis), Essential thrombocythemia, Chronic myeloproliferative disorder, NOS, Refractory anemia with its variants and Myelodysplastic syndrome NOS. This is extremely relevant for registries, since many of these diseases are quite frequent, especially in more advanced age classes.
- ◆ *New cytogenetic nosological definitions*. As in leukemias, new nosological entities are now identified on a cytogenetic basis.
- ◆ *New nosological definitions of "secondary" conditions*. Here, as in leukemias, new therapy-related nosological entities are identified.
- ◆ *Introduction of new nosological definitions*. E.g., chronic eosinophilic and neutrophilic leukemia.

- ◆ *Other diseases remain in /1*. E.g., Lymphoproliferative disorder, NOS and Myeloproliferative disease, NOS.

Disease classifications

These diseases have codes from M-9950 to M-9989: they now all have behavior /3 (except the two mentioned above) and the topography code is always C42.1 There are three subgroups.

- ◆ **Chronic myeloproliferative disorders**
 - ◆ **Polycythemia vera or rubra vera M-9950/3 (ICD-9: 238.4; ICD-10: D45)**
Also known as Vaquez disease, or Chronic erythremia.
 - ◆ **Chronic myeloproliferative disease, NOS M-9960/3 (ICD-9: 238.7; ICD-10: D47.1)**
For cases with poor diagnostic definition.
 - ◆ **Myelosclerosis (or myelofibrosis) with myeloid metaplasia, or Chronic idiopathic myelofibrosis, or Megakaryocytic myelosclerosis or Agnogenic myeloid metaplasia M-9961/3 (ICD-9: 238.7; ICD-10: D47.1).**
 - ◆ **Essential or idiopathic or hemorrhagic thrombocythemia M-9962/3 (ICD-9: 238.7; ICD-10: D47.3).**
 - ◆ **Chronic neutrophilic leukemia M-9963/3 (ICD-9: 205.1; ICD-10: C92.7).**
 - ◆ **Hyper eosinophilic syndrome or chronic eosinophilic leukemia 9964/3 (ICD-9: 205.1; ICD-10: C92.7).**
 - ◆ **Lymphoproliferative disorder, NOS M-9970/1 (ICD-9: 238.7; ICD-10: D47.9).**
 - ◆ **Myeloproliferative disease, NOS M-9975/1 (ICD-9: 238.7; ICD-10: D47.1).**
- ◆ **Myelodysplastic syndromes**
 - ◆ **Refractory anemia, NOS, or without sideroblasts M-9980/3 (ICD-9: 284.9; ICD-10: D46.4, D46.0).**
 - ◆ **Refractory anemia with sideroblasts, or refractory sideroblastic anemia, or refractory anemia with ringed sideroblasts, RARS M-9982/3 (ICD-9: 285.0; ICD-10: D46.1).**
 - ◆ **Refractory anemia with excess blasts (RAEB, RAEB I, RAEB II) M-9983/3 (ICD-9: 285.8; ICD-10: D46.2).**
 - ◆ **Refractory anemia with excess blasts in transformation (RAEB-T) M-9984/3 (ICD-9: 285.8; ICD-10: D46.3).**
 - ◆ **Refractory cytopenia with multilineage dysplasia M-9985/3 (ICD-9: 285.8; ICD-10: D46.3).**

D46.7). With evolution to AML with multilineage dysplasia M-9895/3.

- ◆ **Myelodysplastic syndrome with 5q deletion syndrome (5q-) M-9986/3** (ICD-9: 238.7; ICD-10: D46.7).
- ◆ **Therapy-related myelodysplastic syndrome, NOS (alkylating agents, epipodophyllotoxin) M-9987/3** (ICD-9: 238.7; ICD-10: D46.7). This code should preferably be used in a myelodysplasia secondary to chemotherapy.
- ◆ **Myelodysplastic syndrome, NOS, or preleukemia or preleukemic syndrome M-9989/3** (ICD-9: 238.7; ICD-10: D46.9).

Polycythemia vera or vera rubra (PV, Vaquez disease)

PV is a clonal neoplastic disease originated from pluripotent hematopoietic stem cells. As a consequence, hyperproduction of red blood cells is truly primary, and not correlated to hypoxia or overproduction of erythropoietin. Criteria to distinguish between Polycythemia vera and secondary polycythemia are listed in the inset on the next page. Secondary polycythemia are very common conditions, prevalently due to tissue hypoxia (as in certain chronic lung or heart diseases, hemoglobinopathies, altitude, etc.), hyperproduction of erythropoietin (as in certain malignant neoplasms of the kidney, liver, ovary, etc.), or other renal diseases, adrenocortical diseases, and so forth. Part of PV cases can evolve into myelofibrosis or acute myeloid leukemia (AML). In general, it requires a therapy to contain the level of circulating red cell mass (venesection, cytoreductive therapy) and it is associated with high cardiovascular co-morbidity.

Myelosclerosis with myeloid metaplasia (MMM) or Idiopathic myelofibrosis (IM)

It is a neoplastic disease of the erythrocytic, granulocytic, and – rarely – megakaryocytic series, with bone marrow fibrosis and splenic and hepatic myeloid metaplasia.¹⁷⁻¹⁸

It is considered identical, within code M-9961/3, with Chronic idiopathic myelofibrosis (IM) and requires transfusion therapy. The most common fatal complications of these diseases are infectious diseases, but in about 10% of cases the disease progresses into an AML. Differentiation between the various myeloproliferative syndromes (PV, IM, ET), Chronic myeloid leukemia (CML) and leukemoid reactions is sometimes difficult and clinically complex, resulting at times in confused, conflicting diagnoses that alternate over time and can seriously challenge registries. **Table 7** (page 27) can provide clarification.

Essential thrombocythemia (ET)

Otherwise known as Primary or Chronic idiopathic thrombocythemia, it is a neoplastic disease that affects the pluripotent hematopoietic stem cell, leading to high levels of circulating thrombocytes. Even in this case, there are diagnostic criteria to distinguish between primary and secondary thrombocythemia (see inset on the next page). The latter are quite common and are due to acute conditions (acute hemorrhages, acute infections and inflammations, rebound thrombocytosis, drug responses, etc.) or chronic conditions (iron deficiency, hemolytic anemia, splenectomy, chronic infectious or inflammatory diseases, malignant neoplasms, etc.). Although rarely, ET, too, can progress to AML. In general, it requires a cytoreductive therapy and is associated with high cardiovascular co-morbidity.

DIAGNOSTIC CRITERIA OF PV

Major criteria:

- ❖ increase in RBC mass >25% compared to the average value or hematocrit >60% (men) and >56% (women)
- ❖ absence of causes of secondary erythrocytosis (normal arterial O₂ saturation, no EPO increment)
- ❖ palpable splenomegaly
- ❖ presence of JAK2 V617F mutation or of other cytogenetic abnormalities (excluding bcr/abl) in hematopoietic cells

Minor criteria:

- ❖ thrombocytosis >400 X 10⁹/L
- ❖ neutrophilia (neutrophils >10x10⁹/L; >12.5x10⁹/L in smokers)
- ❖ radiologically documented splenomegaly
- ❖ endogenous erythroid colonies or low levels of EPO

PV is diagnosed if the following criteria are met:

- ❖ the first two major criteria + another major criterion
- ❖ the first two major criteria: + two minor criteria

* American Society of Hematology 2005¹⁹

DIAGNOSTIC CRITERIA IN ET²⁰

Major criteria:

- ❖ thrombocytosis > 600,000/mm³ for at least 2 months
- ❖ presence of mutation JAK2 V617F

Minor criteria:

- ❖ absence of causes of reactive thrombocytosis (normal inflammation markers)
- ❖ no evidence of iron deficiency
- ❖ no evidence of PV
- ❖ no evidence of CML
- ❖ no evidence of myelofibrosis
- ❖ no evidence of myelodysplasia

ET is diagnosed if the following criteria are met:

- ❖ two major criteria + the last four minor criteria (JAK pos.)
- ❖ first major criteria + all six minor criteria (JAK neg.)

Myelodysplastic syndromes (MDS)

MDSs are acquired hematopoietic stem cell disorders, where an atypical clone progressively replaces normal cells. Alterations in all the stages of maturity of the bone marrow are observed, with progressive loss of differentiation: this causes peripheral cytopenia of one or more cell lineages, although the bone marrow is normo- or hypercellular. The myelodysplastic clone is generally unstable, and MDSs therefore progress, after a variable period of time, to acute leukemia. About 40% of cases develop into acute leukemia, but an already significant proportion of subjects dies in a pre-leukemic stage from complications of chronic cytopenia.

MDSs are divided into primary and secondary. Secondary MDS (see code M-9987/3) can be due to exposure to mutagens or leukemogens, but, for the most part, are due to radiation or chemotherapy for primary neoplasms. A FAB classification exists for MDS primaries. Five different types of primary MDS have been identified (**Table 8**, page 28), based on the prevalence of different blood and bone marrow abnormalities (they also include CMML, code M-9945/3).

- ◆ **Refractory anemia (RA):** ringed sideroblasts in the bone marrow <15%;
- ◆ **Acquired idiopathic sideroblastic anemia (AISA), or Refractory anemia with sideroblasts:** ringed sideroblasts >15%;
- ◆ **Refractory anemia with excess blasts (RAEB):** myeloid blasts in peripheral blood up to 5%, in the bone marrow from 5% to 20%;
- ◆ **Refractory anemia with excess blasts in transformation (RAEB-T):** myeloid blasts in peripheral blood over 5%, in the bone marrow from 20% to 30%;
- ◆ **Chronic myelomonocytic leukemia (CMML):** code 9945.

Registration issues in myeloproliferative syndromes and MDS

All conditions in this section are pathologic entities that present reporting problems for cancer registries. In general, they – even substantially – increase the number of cases that requires manual solving (by analytic review of clinical documentation). Since they are fairly common conditions that normally involve the older age groups, it can be assumed that their incidence is nowadays progressively and constantly increasing. As a consequence, their registration using behavior code /3 leads to two fairly significant effects in the registries: on one hand, a clear increase in total cases of hematological neoplasms with malignant behavior (/3), on the other hand, an increase in multiple hematologic neoplasm cases, since, as largely documented above, many of these diseases imply progression towards secondary malignant hematological neoplasms.

Furthermore, a significant part of these diseases are diagnosed, treated, and followed up, even for very long periods of time (decades in certain cases) on an outpatient basis at hospitals or at hematological clinics, thus registries find it very difficult to reconstruct clinical histories of cases and establishing the exact incidence date. These diseases, in addition, appear uncertain and complex to the treating physicians, as well (see many of the tables listing diagnostic criteria). As a consequence, registries frequently encounter diagnostic (or code) inconsistencies or alternative use of terms or codes for the same clinical case over the course of years, resulting in the possibility that the presence of multiple tumors may not be identified. Problems for registries are summarized below.

- ◆ *Difficulty in tracing histopathological diagnosis of cases.* They are often not found in pathological report databases, and even when they are reported, they often represent non-incident cases, since the examinations refer to follow-up procedures, and not to the beginning of the case. In addition, pathology

report databases very often do not report these diseases as /3 yet, but as /1, and this causes further problems. Furthermore, the diagnoses are very often only hematological, on peripheral blood or bone marrow smears, or cytogenetic, or other.

- ◆ *Problems in identifying clinical hospitalizations in HDDs.* ICD-9 codes must be selected that, mostly, are not part of the traditional 140-208 interval largely used by registries. Furthermore, as mentioned above, the first hospitalization does not always match the true incidence of the case, but rather hospitalization is often due to complications, therapy, or specific procedures that are part of a long clinical course, which might have started outside a hospital setting, even several years before. In any case, ICD-9 CM (or ICD-10) codes to be used in HDD casefinding are the following: 238.4, 238.7, 284.9, 285.0 and 285.8 for ICD-9 (D45, D46.0, D46.1, D46.2, D46.3, D46.7, D46.9, D47.1, D47.3 and D47.9 for ICD-10).
- ◆ *Problems in identifying the date of incidence, undefined cases, and prevalence.* For all the above-mentioned reasons, in many cases it is quite difficult to find the correct date of incidence. Many cases have outpatient incidence; in all other cases the general rules used for all other neoplasms must be applied. Since the clinical course of these diseases is usually long, the number of prevalent cases is inevitably high and there will also be a certain number of “undefined” cases (i.e., with undefined date of incidence). In any case, considering the IARC rules which implement ICD-O-3 from 3 the 1998-2002 incidence data, all nosological entities that were previously /1 must be registered and/or re-coded with behavior code /3 starting from 1/1/1998: this obviously means that all cases concerning these diseases, incident up to December 31, 1997, can be treated as prevalent for the registry marking them as “P” or “M”, based on whether they started before or after the registry began registration activity.
- ◆ *Problems in identifying the exact basis of diagnosis, clinically uncertain cases, and erroneous diagnoses or codes.* The number of clinically uncertain or ambiguous cases can be significant; these diseases are almost always encumbered in HDDs by wrong codes, contradictions, alternating codes, and even outright diagnostic mistakes. Obviously, the principle that registries must register and not diagnose is always valid, but in the case of conflicting diagnoses, alternating codes, and so forth, registries must record the clinical diagnosis that is most likely to be the right one, based on the criteria listed in the tables above. Furthermore, the diagnosis of the

highest available quality level should be considered, in the sense that cyto-hematological or histopathological definition must always be considered first, taking into account however that cytogenetic definitions can be fundamental to solve the case in question, as clarified above in the section devoted to nosography.

- ◆ *Problems in identifying cases in death certificates.* Should a death occur from this type of disease as a primary cause, the death certificates for DCI case review should also be examined for the codes given above (ICD-9 and ICD-10), outside the traditional ICD-9 140-208 interval. The problem does not arise in the case of the frequent deaths from a second cancer (e.g., Acute leukemia) with 140-208 codes. Furthermore, it must be remembered that death due to these nosological entities is often marked by the occurrence of a “blast crisis”: unless a clinician explicitly records a diagnosis of leukemia in the clinical record, or a diagnosis of leukemia is not recorded in the ISTAT record, a blast crisis should not be considered by registries as leukemic evolution.
- ◆ *Loss of cases.* As mentioned for CLL, the loss of a certain number of cases appears very likely, for the same reason; this makes it necessary to compare the data every year.

Multiple hematological neoplasms

As previously discussed in several occasions, it is very likely for hematological neoplastic diseases to be sequential in time, i.e., that one may present (and therefore be incident as second neoplasm for a given registry) after a first, separate neoplastic event, which has already been identified by that registry. Furthermore, hematologic cancers can predispose to secondary solid tumors (e.g., in CLL), or they can themselves be secondary to another malignant tumor (e.g., secondary leukemia or myelodysplasia); in any case it must be stressed that not always is the sequence and true isolation of two subsequent hematological neoplastic diseases clear.

Finally, there is the problem of onset of a leukemia secondary to a preceding myelodysplasia or other myeloproliferative disease. Although ICD-O-3 and IARC rules establish that only the first event should be considered for incidence, the subsequent event should also be collected and registered, for at least the following reasons:

- ◆ myeloid leukemia is currently a topical epidemiological issue nowadays, bound to environmental and occupational risk factors;
- ◆ it is therefore necessary to maintain full knowledge of trends and not to lose sight, due to under-registration, for any changes in trends.

For a better understanding of the decisions to make with respect to registration and incident tumors, see Table 4, Chapter 3.

Hodgkin's and non-Hodgkin's lymphoma

UKACR guidelines have clarified that all Hodgkin's and non-Hodgkin's lymphomas should be registered separately, whether synchronous or metachronous, as in any case can be gathered from the IARC rules, since they are divided by two different 3-digit codes of ICD-9. The case of code M-9596/3 (Composite Hodgkin's and non-Hodgkin's lymphoma), which in any case is very rare and potentially ambiguous, is an exception, as registries must record a single tumor.

Mixed codes and highest code rule

As per old IARC rules, in the presence of mixed histology codes, registries should take into account the highest numeric code (e.g., the case of Adenocarcinoma, intestinal type M-8144/3 and Carcinoma, diffuse type M-8145/3 is solved using code M-8145/3). These general rules have been confirmed by ICD-O-3 (Rule K), **but they do not apply to hematologic cancer**, as for hematologic tumors, use of the more specific morphology code is recommended. For instance, if a diagnosis of Malignant lymphoma, large B-cell, diffuse, NOS (M-9680/3) is corrected during review into Mantle cell lymphoma (M-9673/3), code M-9673/3 is considered as basis of diagnosis although it is lower because it is more specific than M-9680/3, which is NOS. In other dubious cases where no differences can be established based on specificity/non-specificity, the most likely code based on clinical-pathological documentation (recurrences, confirmations, etc.) should be used.

The WHO classification²¹ of tumors of the lympho-ematopoietic system is listed in **Table 9** (page 29).

Outpatient incidence date

A very large number of hematological neoplasms is diagnosed outside a hospital setting. The following pathologic entities have relevant proportions of cases found in an outpatient setting.

- ◆ Low grade or chronic lymphomas (mainly Small B-cell lymphocytic lymphoma, CLL correlated, mycosis fungoides, etc.);
- ◆ Multiple myeloma (in non advanced stages, or smoldering, etc.), other immunoproliferative diseases, etc.;
- ◆ Prevalently chronic leukemias (e.g., CLL, CML, CMML, hairy cell leukemia, etc.);
- ◆ Chronic myeloproliferative diseases and MDS (e.g., PV, MMM or IM, ET, RA, RARS, RAEB, etc.);

it is believed that over 50% of cases today are diagnosed outside a hospital setting.

The following are examples of registration of these cases:

- ◆ having identified a case, the registry reconstructs the case history, which began on a precise outpatient date, which is more than three months before any other histopathological or clinical data;
- ◆ in the case in question, cytology and pathology data are missing from the databases, or at any rate the data are at least three months subsequent to the established outpatient date;
- ◆ in the case in question, clinical data are missing from the HDD, or at any rate the data are at least three months subsequent to the established outpatient date.

Actually, in a great number of cases the outpatient date of diagnosis precedes the first hospitalization recorded in HDD or the first histopathological diagnosis not just by three months, but by several years. It is therefore evident that the traditional criteria used to establish the date of incidence (date of first positive cyto-histological sampling or, if absent, date of first clinical hospitalization) are in these cases insufficient to establish the true time of onset of the disease.

In conclusion, whenever a registry identifies an initial, certain outpatient date of disease onset, **which is at least 3 months earlier than any other date**, the registry is allowed to use that date as date of incidence for that case.

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Tables

Table 1. Ann Arbor staging

BACK

Stage	Definition																										
I	<ul style="list-style-type: none"> ❖ involvement of a single lymph node region (I), or: ❖ localized involvement of a single organ or extralymphatic site with no lymph node involvement (IE(rare in Hodgkin's lymphoma)) 																										
II	<ul style="list-style-type: none"> ❖ involvement of two or more lymph node regions on the same side of the diaphragm (II), or: ❖ localized involvement of an extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE); the number of regions involved may be indicated by a subscript (e.g., II3). 																										
III	<ul style="list-style-type: none"> ❖ involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S). 																										
IV	<ul style="list-style-type: none"> ❖ diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; ❖ or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s); ❖ or any involvement of the liver or bone marrow, or nodular involvement of the lung(s). <p>The location of stage IV disease is further identified by specifying the site according to the following notations:</p> <table style="margin-left: 40px; border: none;"> <tr><td>Spleen</td><td>S</td></tr> <tr><td>Lung</td><td>L</td></tr> <tr><td>Bone marrow</td><td>M</td></tr> <tr><td>Liver</td><td>H</td></tr> <tr><td>Pericardium</td><td>Pcard</td></tr> <tr><td>Pleura</td><td>P</td></tr> <tr><td>Waldeyer's ring</td><td>W</td></tr> <tr><td>Osseus</td><td>O</td></tr> <tr><td>Gastrointestinal</td><td>GI</td></tr> <tr><td>Skin</td><td>D</td></tr> <tr><td>Central nervous system</td><td>B</td></tr> <tr><td>Soft tissues</td><td>Softs</td></tr> <tr><td>Thyroid</td><td>Thy</td></tr> </table>	Spleen	S	Lung	L	Bone marrow	M	Liver	H	Pericardium	Pcard	Pleura	P	Waldeyer's ring	W	Osseus	O	Gastrointestinal	GI	Skin	D	Central nervous system	B	Soft tissues	Softs	Thyroid	Thy
Spleen	S																										
Lung	L																										
Bone marrow	M																										
Liver	H																										
Pericardium	Pcard																										
Pleura	P																										
Waldeyer's ring	W																										
Osseus	O																										
Gastrointestinal	GI																										
Skin	D																										
Central nervous system	B																										
Soft tissues	Softs																										
Thyroid	Thy																										
Additional designations unrelated to site:																											
A	absence of systemic symptoms																										
B	presence of systemic symptoms (fever, night sweats, unexplained loss of 10% or more of body weight in the 6 months preceding admission)																										
X	bulky disease: widening of the mediastinum >1/3 or nodal mass >10 cm																										

Table 2. Morphological and clinical types of chronic lymphocytic leukemia³
(modified with ICD-O-3 codes)

BACK

B-cell lymphocytic leukemia	T-cell lymphocytic leukemia
B-cell chronic lymphocytic leukemia	T-cell chronic lymphocytic leukemia
ICD-O-3: 9823/3	ICD-O-3: 9823/3
B-cell prolymphocytic leukemia	T-cell prolymphocytic leukemia
ICD-O-3: 9833/3	ICD-O-3: 9834/3
Splenic lymphoma with villous lymphocytes	Sézary's syndrome
ICD-O-3: 9689/3	ICD-O-3: 9701/3
Hairy cell leukemia	Large granular lymphocytic leukemia
ICD-O-3: 9940/3	ICD-O-3: 9831/3
Plasma cell leukemia	Precursor cell lymphoblastic lymphoma, NOS
ICD-O-3: 9733/3	ICD-O-3: 9827/3

Table 3. Chronic lymphocytic leukemia clinical staging criteria
BACK

Staging according to Rai (1975) ⁶			
Stage	Clinical criteria		Risk category
0	bone marrow and blood lymphocytosis		low
I	diffuse lymphocytosis and enlarged nodes		intermediate
II	lymphocytosis with enlarged spleen and/or liver		intermediate
III	lymphocytosis with anemia (Hb <11 g/dL) with or without enlarged liver/spleen/nodes		high
IV	lymphocytosis with thrombocytopenia (PLT <100x10 ⁹ /L) with or without anemia and/or enlarged liver/spleen/nodes		high
Staging according to Binet (1981) ⁷			
Stage 0	Hematological criteria		Clinical criteria
A	Hb ≥10g/dL	PLT ≥100,000 mm ³	<3 sites involved
B	Hb ≥10g/dL	PLT ≥100,000 mm ³	≥3 sites involved
C	Hb <10g/dL	PLT <100,000 mm ³	any number of sites
<i>Note: median survival for LLC cases is closely correlated to Rai and Binet staging</i>			

Table 4a. Diagnostic criteria for multiple myeloma and MGUS¹¹
BACK

In 2003 the International Myeloma Working Group identified the following diagnostic criteria:¹¹

Symptomatic myeloma

1. clonal plasma cell >10% on bone marrow biopsy or (in any amount) biopsy of other tissues (plasmacytoma)
2. monoclonal protein (paraproteinemia) in the serum or urine
3. evidence of damage in target organs (related organs or tissue impairment, ROTI):
 - ❖ hypercalcemia (calcemia >2.75 mmol/L)
 - ❖ kidney failure attributable to myeloma
 - ❖ anemia (Hb <10 g/dL)
 - ❖ bone lesions (osteolytic or osteoporosis with compression fractures)
 - ❖ frequent severe infections (>2/year)
 - ❖ amyloidosis of other organs
 - ❖ hyperviscosity syndrome

Asymptomatic myeloma

1. paraproteinemia <30 g/L
- and/or:
2. clonal plasma cells <10% in bone marrow biopsy
- and:
3. no involvement of tissues or organs associated to myeloma*

*correlated syndromes include solitary plasmacytoma, plasma cell dyscrasia (where only the antibodies produce symptoms, as in amyloidosis), and POEMS syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorders and skin diseases)

Monoclonal gammopathy of undetermined significance (MGUS)

1. paraproteinemia <30 g/L
- and/or:
2. clonal plasma cells <10% in bone marrow biopsy
- and:
3. no involvement of tissues or organs associated to myeloma

Diagnosis was previously based on the following parameters:
Major criteria

- I. histological diagnosis of plasmacytoma
- II. bone marrow plasmacytosis >30%
- III. protein M in serum (IgG >3.5 g/dL or IgA >2 g/dL) and/or urine (Bence-Jones proteinuria Jones – κ or λ chains – >1g/24 hours)

Minor criteria

- a. bone marrow plasmacytosis between 10 and 30%
- b. protein M lower than the III major criterion
- c. osteolytic lesions
- d. suppression of normal Ig (IgG <0.6 g/dL, IgA <0.1 g/dL, IgM <0.05 g/dL)

For the diagnosis of myeloma, one major criterion + one minor criterion (I+B, I+C, I+d), (II+b, II+c, II+d), (III+a, III+c, III+d), or three minor criteria, including the first two (a+b +c, a+bd), were needed.

Table 4b. MGUS, multiple myeloma and other conditions: differential diagnosis¹²
BACK

Data field	MGUS	Smoldering myeloma	Multiple myeloma	Waldenström's macroglobulinemia	Primary amyloidosis
bone marrow plasma cells (%)	<10	≥10	≥10	>10 (lymphoplasmacytoid cells)	<10
	and	and/or	and/or	and	and
monoclonal protein level (g/dL)	<3	≥3	≥3	>3	<3
clinical manifestations	absent	absent	present*	present*	present*

*clinical signs present according to basic disease

Table 5. Myeloma staging criteria

BACK

International Staging System (ISS, 2003) published by the International Myeloma Working Group ¹²		
Stage	Criteria	
I	$\beta 2M^* < 3.5 \text{ mg/L} + \text{albumin} \geq 3.5 \text{ g/dL}$	
II	$\beta 2M < 3.5 \text{ mg/L} + \text{albumin} < 3.5 \text{ g/dL}$ or: $\beta 2M \text{ between } 3.5 \text{ and } 5.5 \text{ mg/L}$	
III	$\beta 2M > 5.5 \text{ mg/L}$	
* $\beta 2$ -microglobulin		
Multiple myeloma staging according to Durie and Salmon (1975) ¹³		
Stage 0	Criteria	Plasma cell mass (cells x 10 ¹² /m ²)
I	all of the following: ❖ hemoglobin >10 g/dL ❖ serum calcium value normal (<12 mg/dL) ❖ bone X-ray: normal bone structure or solitary bone plasmacytoma ❖ CM IgG <5 g/dL, IgA <3 g/dL ❖ Bence-Jones protein <4 g/24 h	<0.6 (low)
II	cases not classifiable in stage I or III.	0.6-1.2 (intermediate)
III	one or more of the following criteria: ❖ hemoglobin <8.5 g/dL ❖ serum calcium >12 mg/dL ❖ more than three bone lesions and/or major pathologic fractures ❖ CM IgG <7 g/dL, IgA <5 g/dL ❖ Bence-Jones protein >12 g/24 h	IA, IB, IIA, IIB, IIIA, IIIB staging
Subclassifications A and B	A = serum creatinine <2mg/dL B = serum creatinine >2mg/dL	

Table 6. FAB classification of ALLs and AMLs

BACK

ALL				
FAB subtype	Morphology (May Grumwald)	Frequency (%)	Distribution by age	
L1	❖ small blasts; ❖ scanty cytoplasm	10-25	more frequent in children	
L2	❖ large, heterogeneous blasts ❖ presence of one or more nucleoli	70-80	more frequent in adults	
L3	❖ vacuolated basophilic blasts ❖ nucleoli and nuclear vacuoles	1-5	more frequent in children	
AML				
FAB subtype	Bone marrow morphology	Cytochemistry	Cell antigens	Frequency (%)
M1	myeloblasts >90%	❖ myeloperoxidase positive ❖ positive Sudan black B stain	CD13; CD31; CD33; CD34; HLA-DR	15-20
M2	myeloblasts <90%	❖ myeloperoxidase positive ❖ positive Sudan black B stain ❖ positive for esterase NaF resistant	CD13; CD15; CD31; CD33; HLA-DR	25-35
M3	heavily granulated blasts with Auer rods	❖ myeloperoxidase positive ❖ positive Sudan black B stain	CD13; CD31; CD33	3-8
M3v	blasts with fine bilobed or multilobed granules	❖ myeloperoxidase positive ❖ positive Sudan black B stain	CD13; CD31; CD33, CD2	1
M4	myeloblasts <80% monoblasts >20%	❖ myeloperoxidase positive ❖ positive Sudan black B stain ❖ positive for esterase NaF resistant and inhibited	CD11c; CD13; CD14; CD15; CD31; CD33; HLA-DR	20-25
M5a	monoblasts >80%	positive for esterase, NaF inhibited	CD11b; CD11c; CD13; CD14, CD15; CD31; CD33; CD68; HLA-DR	5-10
M5b	❖ monoblasts ❖ promonoblasts ❖ monocytes	positive for esterase, NaF inhibited	CD11b; CD11c; CD13; CD14, CD15; CD31; CD33; CD68; HLA-DR	2-6
M6	❖ erythroblasts >50% ❖ myeloblasts >30%	❖ PAS positivity ❖ myeloperoxidase positive ❖ positive Sudan black B stain	glycophorin-A	3-5
M7	❖ lymphoblast-like blasts >30% ❖ myelofibrosis	platelet peroxidase	CD41; CD42; CD61; glycoprotein IIB/IIIA	1-3

Table 7. Differentiation between CML, various myeloproliferative syndromes, and leukemoid reaction
BACK

Features	CML	PV	IM	ET	Leukemoid reaction
leukocytosis	+++	+	+	+	+
enlarged spleen	++	+	+++	+	–
peripheral blood eosinophilia	++	+	+	+	–
peripheral blood basophils	++	+	+	+	–
thrombocytosis	++	+	+	+++	–
bone marrow fibrosis	++	+	+++	+	–
leukocyte alkaline phosphatase	dim./absent	normal	inc./norm.	inc./norm.	normal
Ph chromosome†	+	–	–	–	–

Table 8. MDS: features and prognosis
BACK

FAB subtype	Bone marrow blast count (%)	Bone marrow sideroblasts (%)	Grade of bone marrow dysplasia.	Development of acute leukemia (%)	Median survival (months)
RARS	<5	>15	+	1-5	60
RA	<5	<15	+	15	40
RAEB	5-20	data field	++	40-50	12-15
RAEB-T	20-30	data field	++	90	5-10
CMML	1-20	data field	++	30	20

Table 9. WHO: classification of tumors of the lymphohematopoietic system²¹

BACK

Hodgkin's lymphoma		Mast cell tumors	
9651/3	Hodgkin's lymphoma, lymphocyte-rich	9740/1	Mastocytoma, NOS
9652/3	Hodgkin's lymphoma, mixed cellularity, NOS	9740/3	Mast cell sarcoma
9653/3	Hodgkin's lymphoma, lymphocyte depletion, NOS	9741/1	Indolent systemic mastocytosis
9659/3	Hodgkin's lymphoma, nodular lymphocyte predominance	9741/3	Malignant mastocytosis
9650/3	Hodgkin's lymphoma	9742/3	Mast cell leukemia
9663/3	Hodgkin's lymphoma, nodular sclerosis, NOS		
B-cell lymphomas		Neoplasms of histiocytes and accessory lymphoid cells	
<i>precursor cell lymphomas</i>		<i>macrophage/histiocytic neoplasms</i>	
9728/3	Precursor B-cell lymphoblastic lymphoma	9755/3	Histiocytic sarcoma
9836/3	Precursor B-cell lymphoblastic leukemia		
<i>mature B-cell lymphomas</i>		<i>dendritic cell neoplasms</i>	
9670/0	Malignant lymphoma, small B lymphocytic, NOS	9751/1	Langerhans cell histiocytosis, NOS
9671/3	Malignant lymphoma, lymphoplasmacytic	9756/3	Langerhans cell sarcoma
9673/3	Mantle cell lymphoma	9757/3	Interdigitating dendritic cell sarcoma
9678/3	Primary effusion lymphoma	9757/1	Interdigitating dendritic cell tumor
9679/3	Mediastinal large B-cell lymphoma	9758/1	Follicular dendritic cell tumor
9680/3	Malignant lymphoma, large B-cell, diffuse, NOS	9758/3	Follicular dendritic cell sarcoma
9687/3	Burkitt's lymphoma, NOS		
9689/3	Splenic marginal B-zone lymphoma	Acute myeloid leukemias	
9690/3	Follicular lymphoma, NOS	<i>with cytogenetic abnormalities</i>	
9699/3	Marginal zone B-cell lymphoma, NOS (MALT)	9866/3	Acute promyelocytic leukemia t(15;17)(q22;q11-12) (FAB M3)
9731/3	Plasmacytoma, NOS	9871/3	Acute myeloid leukemia with abnormal marrow eosinophils (FAB M4Eo)
9732/3	Multiple myeloma	9896/3	Acute myeloid leukemia t(8;21)(q22;q22)
9734/3	Plasmacytoma, extramedullary (not occurring in bone)	9897/3	Acute myeloid leukemia, 11q23 abnormalities
9823/3	B-cell chronic lymphocytic leukemia / small lymphocytic lymphoma	<i>with multilineage dysplasia</i>	
9826/3	Burkitt's cell leukemia	9895/3	Acute myeloid leukemia with multilineage dysplasia
9833/3	Prolymphocytic leukemia, B-cell type	<i>therapy-related</i>	
9940/3	Hairy cell leukemia	9920/3	Therapy-related acute myeloid leukemia, NOS
<i>of uncertain malignant potential</i>		<i>not otherwise classified</i>	
9766/1	Angiocentric immunoproliferative lesion (lymphomatoid granulomatosis)	9840/3	Acute myeloid leukemia, M6 type
9970/1	Lymphoproliferative disorder, NOS	9867/3	Acute myelomonocytic leukemia (FAB M4)
		9870/3	Acute basophilic leukemia
		9872/3	Acute myeloid leukemia, minimal differentiation (FAB M0)
		9873/3	Acute myeloid leukemia without maturation (FAB M1)
		9874/3	Acute myeloid leukemia with maturation (FAB M2)
		9891/3	Acute monocytic leukemia (FAB M5)
		9930/3	Myeloid sarcoma
		9931/3	Acute panmyelosis with myelofibrosis
		<i>of ambiguous lineage</i>	
		9805/3	Acute biphenotypic leukemia
T and NK cell lymphomas			
<i>precursor cell lymphomas</i>			
9727/3	Precursor cell lymphoblastic lymphoma, NOS		
9729/3	Precursor T-cell lymphoblastic lymphoma		
9837/3	Precursor T-cell lymphoblastic leukemia		
<i>mature T and NK cell lymphomas</i>			
9700/3	Mycosis fungoides		
9701/3	Sézary's syndrome		
9702/3	Mature T-cell lymphoma, NOS		
9705/3	Angioimmunoblastic T-cell lymphoma		
9708/3	Subcutaneous panniculitis-like T-cell lymphoma		
9714/3	Anaplastic large cell lymphoma, T-cell and Null cell type		
9716/3	Hepatosplenic gamma-delta cell lymphoma		
9717/3	Intestinal T-cell lymphoma		
9718/3	Primary cutaneous CD30+ T-cell lymphoproliferative disorder		
9719/3	NK/T-cell lymphoma, nasal and nasal-type		
9827/3	Precursor cell lymphoblastic lymphoma, NOS (HTLV-1 positive)		
9831/3	T-cell large granular lymphocytic leukemia		
9834/3	Prolymphocytic leukemia, T-cell type		
9948/3	Aggressive NK-cell leukemia		

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Chronic myeloproliferative diseases

9875/3	Chronic myelogenous leukemia, BCR/ABL positive
9950/3	Polycythemia vera
9961/3	Myelosclerosis with myeloid metaplasia
9962/3	Essential thrombocythemia
9963/3	Chronic neutrophilic leukemia
9964/3	Hypereosinophilic syndrome
9985/3	Refractory cytopenia with multilineage dysplasia

Myelodysplastic/myeloproliferative diseases

9945/3	Chronic myelomonocytic leukemia, NOS
9876/3	Atypical chronic myeloid leukemia, BCR/ABL negative
9946/3	Juvenile myelomonocytic leukemia
9975/3	Myelodysplastic/myeloproliferative disease, unclassifiable

Myelodysplastic syndromes

9980/3	Refractory anemia
9982/3	Refractory anemia with sideroblasts
9985/3	Refractory cytopenia with multilineage dysplasia
9983/3	Refractory anemia with excess blasts
9986/3	Myelodysplastic syndrome with 5q deletion (5q-) syndrome
9989/3	Myelodysplastic syndrome, NOS
