

RARE HAEMATOLOGICAL CANCERS

PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

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PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

A. Type of cancer

Rare haematological malignancies are arbitrarily defined as $< 6/100\ 000$ habitants and cover thus all malignant hemopathies excepted diffuse large B cell lymphomas, follicular non Hodgkin lymphomas, chronic lymphocytic leukemias and multiple myeloma.

Rare lymphoid malignancies (LM) include

1. All other Mature B cell neoplasms
2. All diseases among the mature T and NK cell neoplasms
3. All diseases among the precursor lymphoid B and T neoplasms
4. Hodgkin lymphoma
5. All diseases among the hystiocytic and dendritic cell neoplasms
6. Post transplants lymphoproliferative disorders
7. AL amyloidosis

Rare myeloid malignancies (MM) are defined as

1. All diseases among the myeloproliferative Neoplasms
2. All diseases among the myeloid and lymphoid neoplasms with eosinophilia
3. All diseases among the myelodysplastic/Myeloproliferative Neoplasms
4. All diseases among the Myelodysplastic syndromes
5. Acute Myeloid leukemias
6. Acute Leukemias with ambiguous lineage

Cutaneous T-cell lymphomas are discussed in another document “the organisation of care for patients with primary cutaneous lymphomas” (cf Working group Skin Tumours).



B. Short description of the cancer

New statistics on malignant hemopathies have recently been collected by the National Cancer Registry and haematological cancers represent – in 2010 - 5 885 new cases, meaning 10% of all malignancies. Lymphoid malignancies and myeloid represent respectively 70% (4 000 cases) and 30% (1 800 cases).

These disorders (annexe 1) represent a real challenge for haematoma-oncologists, not only in terms of pathological diagnoses (now very complex with the integration of morphological, phenotypical, cytogenetical and molecular data) but also in terms of imaging (requiring true experts in the interpretation of ¹⁸F-DG-PET/CT scan) and in terms of therapeutic approaches (including chemotherapy, radiotherapy, immunotherapy, targeted therapy, transplantation and the management of curable diseases in older patients).

These malignant hemopathies require today a comprehensive approach by a multidisciplinary team to guarantee to the patient the optimal healthcare, the access to the most modern therapies and thus the best overall survival.

C. Model of care pathway suggested for adult patients with rare haematological cancers

Model of care pathway	Preferred models
<p>1. <u>Model 1: Reference Centres exclusively (from diagnosis to follow-up).</u> Once there is a suspicion of the cancer type described in A or the cancer type described in A has been diagnosed, the patient should be referred to a Reference Centre. A network with other Reference centres or with specific experts working in other centres is encouraged.</p>	<p># 3 - # 7 # 12 - # 13 N= +/- 700 cases /yr</p>
<p>2. <u>Model 2 : The Reference Centre is reviewing the pathological diagnosis,</u> the imaging and a decision is taken by the Reference MOC. In (Phone/videoconf) relationship with the Peripheral Centre referring the patient for advice. The treatment and the follow-up are then taken in charge by the haematologist of the patient.</p>	<p># 1 – 2 – 4 – 5 – 6 – 8 – 9 – 10 – 11 N= +/- 2 500 cases /yr</p>
<p>3. <u>Model 3: The Reference Centre is reviewing the pathological diagnoses only.</u> Beside true rare malignancies requiring a specific program for their management, we would like to stress that the most frequent lymphomas such as “diffuse large B cell” or “follicular” lymphomas include many “borderline” cases requiring a specific expertise in morphology and molecular pathology, in order to identify rare entities requiring more aggressive or more specific treatments. That’s the reason why we have proposed a third categorie “C” where all lymphomas are reviewed by a panel of haemato-pathologists as proposed in the KCE pathological WG for haematological malignancies.</p>	<p>Diffuse large B cell and follicular lymphomas</p>
<p>Imaging, MOC and therapeutical approaches are performed by the haematologist of the patient in their own centre with a multidisciplinary team.</p>	



D. Phase(s) of the clinical pathway for which Reference Centres are required

Phase of the Clinical Pathway	Reference Centre	Peripheral Centre
Comprehensive AP diagnosis	#1 – 13 + diffuse large B cell and follicular lymphomas	multiple myeloma, chronic lymphocytic leukemias (n ≈1 500 pts/yr)
Diagnostic confirmation (with medical imaging)	# 1 to 13	diffuse large B cell and follicular lymphomas, multiple myeloma, chronic lymphocytic leukemias
MOC*	# 1 to 13	diffuse large B cell and follicular lymphomas, multiple myeloma, chronic lymphocytic leukemias
Therapeutic modalities		
- chemotherapy	# 3 – 7 - 12 - 13	All others
- radiation therapy	# 4	All others
- targeted therapy	# 3 – 7 - 12 - 13	All others
transplantation	# 3 – 7 - 12 - 13 (or when indicated) Allotransplant JACIE ^a centres	Autotransplant JACIE Centres
Follow-up	# 3 - 7 - 12 - 13	# 1 – 2 – 4 – 5 – 6 – 8 – 9 – 10 # 11

^a JACIE: The Joint Accreditation Committee-ISCT (Europe) & EBMT is a non-profit body established in 1998 for the purposes of assessment and accreditation in the field of haematopoietic stem cell (HSC) transplantation. JACIE's primary aim is to promote high quality patient care and laboratory performance in haematopoietic stem cell collection, processing and transplantation centres through an internationally recognised system of accreditation. As of January 2013, 9 centres were JACIE accredited and some others are in the process in Belgium.



Multidisciplinary Oncological Consult (MOC) in a Reference Centre includes :*

1. Three full time equivalent (FTE) clinical hematologists (+ contact by teleconference with the local haematologist)
2. A radiotherapist with expertise in onco-hematology
3. A lab hematologist with expertise in marrow cytology and flow cytometry
4. A hemato-pathologist (recognized by peers as such)
5. A nuclearist working in a department accredited for PET/CT) (present or “web-based imaging platform” during MOC)
6. A geneticist working in an accredited cytogenetics department (available by teleconference during the MOC)
7. A clinical biologist or pathologist or geneticist for molecular hematological analyses (available by teleconference during the MOC)
8. An expert in allogenic transplantation from a JACIE accredited Centre (present during the MOC)
9. A program for clinical research (ongoing Ethics committee-approved clinical trials and data nurse unit)

Comprehensive AP review (Central Review) by hemato-pathologist in a Reference Centre is justified by

1. Complexity of morphology, phenotype and molecular data in most of the rare disorders.
2. Facilities and equipment required to perform new cytogenetics/molecular tests
3. Expertise required both to perform the cell or tissue sampling and to interpret the results
4. A network of pathologists with specific interest in haemato-pathology from different institutions must be put into place to allow interactive discussion.
→ **Practical organisation has been described by the WG on pathology with special emphasis for “hematopathology” with T. Tousseyn, P. de Paepe and Y. Theate (annex 2)**

Diagnostic confirmation has to be performed in a Reference Centre because of

1. Complexity of the histology and sophisticated new molecular techniques that are mandatory
2. Complexity of the diagnosis in terms of morphology, phenotype, cytogenetics and molecular techniques
3. Facilities and equipment are required: morphology, flow cytometry
4. Expertise required both to interpret the results of imaging techniques such as ¹⁸F¹⁸FDG-PET/CT (a reference nuclear department should fulfil the national criteria of AR 2007.03.04 or European accreditation)
5. Complexity in integrating clinical data, imaging (¹⁸F¹⁸FDG-PET/CT...), morphology, phenotype, cytogenetics and molecular techniques to provide an accurate diagnosis.

Centralized MOC and treatment decision in a Reference Centre is justified by

1. Complexity in integrating clinical data, imaging (PET/CT...), morphology, phenotype, cytogenetics and molecular techniques to provide an accurate diagnosis with appropriate prognostic stratification.



2. Complexity in integrating all therapeutic approaches (chemotherapy, immunotherapy, targeted therapy, transplantation, radiotherapy...) to determine the best treatment plan for each patient, requiring a true multidisciplinary approach (Cf section 1)
3. To guaranty to the patient the optimal approach in a rare disease
4. To provide access to new drugs (in clinical trial, if available in Belgium)

Therapeutic modalities

- Model 2 and 3: A hospital with a program in oncology is able to administer chemotherapy or biotherapy
- A Model 1 reference centre for treatment is only required for rare diseases reported in # 3, # 7, #12, #13. Because of :
 - o Complexity of the chemotherapy and transplantation, new therapeutic strategies (immunotherapy, vaccines, targeted treatments...), techniques to spare organs and preserve function (severe neutropenia), identification of bacterial, fungal, viralpathogens
 - o Facilities and equipment required such as a “Sterile Unit”
 - o Care covered 7 days/week for clinical, radiological and biological procedures, for the treatment of chemotherapy-induced neutropenia or other side effects
 - o A team with at least 3 FTE experts in onco-hematology to guaranty interactions and coverage of holidays or meeting periods
 - o A team with specifically trained nurses and paramedical familiar with neutropenic and immunosuppressed patients
 - o Full supportive care services available on-site (therapeutic apheresis, neurology, pain clinic, palliative care, ...) and/or through formal collaborations (sperm storage, ovary cryopreservation...)
 - o An allogeneic JACIE-accredited centre for all allogeneic transplants
- In Hodgkin’s Lymphoma, a “reference radiotherapy service” should include: at least 2 linear accelerators with on board imaging, CT-simulation, appropriate immobilisation devices, treatment planning system allowing IMRT and/or IMAT, access to nuclear imaging for fusion. Radiotherapy should be restricted to one site, with at least 3 FTE radiation oncologists, of whom at least 1 has specific expertise in treating haematological diseases. According to protocols using involved field or node radiotherapy, experience with these techniques is required (e.g. by earlier participation to trials).
- There are two special other situations:
 - o For Total Body Irradiation (TBI), we refer to the requirements for transplantation centres.
 - o For total skin irradiation, there are only a few centres offering this technique in Belgium.

Follow-up: only in Reference Centre for # 3, # 7, # 12, # 13 because of :

1. Close knowledge of the patient’s diagnosis, treatment pathway, history of comorbidities and post-therapeutic complications, personality and environment
2. Complexity of the surveillance
3. Medical expertise required in short term and long term Side effects of new drugs



E. General and specific criteria for Reference Centres

A Reference Centre is defined by specific requirements in terms of human resources and infrastructure

1. Three full time equivalent (FTE) clinical hematologists
2. A radiotherapist with expertise in onco-hematology
3. Two lab hematologists with expertise in marrow cytology and flow cytometry
4. A hemato-pathologist (recognized by peers as such)
5. A nuclearist working in a department with national or European accreditation for PET/CT (present or linked through a “web-based imaging platform” during the MOC)
6. A close collaboration with a geneticist working in an accredited cytogenetics department (available by teleconference during the MOC)
7. A clinical biologist or pathologist for molecular hematological analyses (available by teleconference during the MOC)
8. An expert in allogenic transplantation from a JACIE accredited Centre (present during the MOC)
9. A department equipped for medical and nursing care of immunosuppressed hematological patients (« sterile unit »)
10. A program for clinical research (ongoing Ethics committee-approved clinical trials and data nurse unit)
11. A nurse’s team qualified in oncology and with continuous training
12. An ICU equipped for immunosuppressed patients
13. A laboratory equipped for the diagnosis of bacterial, fungal, viral infections in immunosuppressed patients
14. A blood bank timely providing blood product support, including irradiated products and aphaeresis platelet transfusions
15. A “reference radiotherapy service” for treatment of Hodgkin’s Lymphoma and Total Body Irradiation (TBI)
16. A blood bank timely providing blood product support, including irradiated products and apheresis platelet transfusions
17. Services performing urgent dialysis and therapeutic apheresis (plasmapheresis and cytappheresis)

Other requirements

1. Reasonable waiting and throughput times with regard to first outpatients’ visit, admission, and tests/treatment
2. Continuity of care (care covered 7 days a week by specialised staff, agreements concerning the continuity of care...)
3. Support services for the patient (identification of a care coordinator, support for patient's information, link with patient's associations, specific website for patients / professionals...)
4. National and international networking with other Reference Centres (appropriate arrangements for referrals within Belgium and from/to other EU countries if applicable)
5. Shared care: formal links with other hospitals, specialists and general practitioners (Consideration of E-Health solutions -e.g. shared case management systems, expert systems for tele-expertise and shared repository of cases-).



6. Organisation of collaborations to assure the continuity of care between childhood, adolescence and adulthood, if relevant.
7. Organisation of collaborations to assure the continuity of care between all stages of the disease.

Minimal volume of patients

No consensus could be obtained because of the rarity of most of these entities.

Quality Assurance :

A reference centre has Written procedures (SOP) for

1. Diagnostic and treatment guidelines in malignant hemopathies
2. Quality indicators and quality objectives in terms of structure, treatments, outcome
3. Exhaustive and reliable information sent to National Cancer Registry
4. Compliance with existing guidelines and documentation of deviations from guidelines
5. Annual activity report ensuring transparency (e.g. number of new patients / type of cancer, diagnostic, treatment and outcome data, specific protocols for reporting and recording complications..)

Research and other scientific activities

A Reference Centre has to demonstrate:

1. Involvement in clinical studies (RCTs, Cohort studies, translational studies)
2. Publications in peer-reviewed journals, grants, ...
3. Link with a tumour biobank
4. Development of clinical practice guidelines for diagnosis , work up and treatment.

Educational activities

should include initial and continuous medical training of physicians and “paramedics”, organization of scientific meetings,... is an additional value but not mandatory to be a Reference Centre.



Additional comments

The current management of rare haematological cancers in Belgium may be quite different from the model that is proposed here.

A transition period of 3 to 5 years seems reasonable to allow adapting the organisation of care to deal with rare haematological cancers according to this model. It is equally important that after this period, the model is re-evaluated and necessary adaptations are discussed again. Reference centres (or rather reference networks) will need to arrange themselves according to the requirements mentioned above. Peripheral centres will need to set up collaborations with reference centres to offer the patients efficient and dedicated care in a reasonable time frame. In order to increase the chances that this model can be successfully implemented, it is highly recommended that some incentive or other form of facilitation is created to encourage referral and collaboration between peripheral and reference centres and/or between different sites of reference networks.

Finally, before such model is implemented, this proposal has to be thoroughly discussed with the Belgian Hematological Society. Members of the BHS recognize that a comprehensive reorganization of the hemato-oncology in Belgium with the ultimate goal to improve care for patients is a valid goal. The BHS board's point of view is the following:

1. We recognize that the organization of the hemato-oncology in Belgium can be improved to the benefit of the patients. This relates to the complexity of diagnosis and treatment and to the increasing subclasses and different stages of the diseases which makes them all rare enough to be the subject of a multidisciplinary approach including experts in all diagnostic and therapeutic approaches.
2. We feel that such reorganization including the definition of rare entities as well as the definition and function of reference centres requires more time and discussion and must be based on a general consensus involving university as well as non-university centres.
3. The BHS is the only organization entitled to represent the field of hematology in Belgium and should be involved in any initiative with potential major impact on the practice of hematology in Belgium.
4. Only recognized clinical hematologists should be entitled to take care of hemato-oncological diseases according to the definitions of the officially defined competence.
5. The pathology review is crucial in our practice and should be a priority.
6. A good spirit of collaboration and confidence between all stakeholders in the hemato-oncology should be preserved with respect for the specific and complementary functions of both university and non-university centres.



ANNEXE #1 : WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Swerdlow SH, et al., Lyon, France: IARC Press; 2008.

WHO Classification of tumours of haematopoietic and lymphoid tissues

MYELOPROLIFERATIVE NEOPLASMS		MYELOYDYSPLASTIC SYNDROMES	
Chronic myelogenous leukaemia, <i>BCR-ABL1</i> positive	9875/3	Refractory cytopenia with unilineage dysplasia	
Chronic neutrophilic leukaemia	9963/3	Refractory anaemia	9980/3
Polycythaemia vera	9950/3	Refractory neutropenia	9991/3
Primary myelofibrosis	9961/3	Refractory thrombocytopenia	9992/3
Essential thrombocythaemia	9962/3	Refractory anaemia with ring sideroblasts	9982/3
Chronic eosinophilic leukaemia, NOS	9964/3	Refractory cytopenia with multilineage dysplasia	9985/3
Mastocytosis		Refractory anaemia with excess blasts	9983/3
Cutaneous mastocytosis	9740/1	Myelodysplastic syndrome associated with isolated del(5q)	9986/3
Systemic mastocytosis	9741/3	Myelodysplastic syndrome, unclassifiable	9989/3
Mast cell leukaemia	9742/3	Childhood myelodysplastic syndrome	
Mast cell sarcoma	9740/3	<i>Refractory cytopenia of childhood</i>	9985/3
Extracutaneous mastocytoma	9740/1		
Myeloproliferative neoplasm, unclassifiable	9975/3		
MYELOID AND LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND ABNORMALITIES OF <i>PDGFRA</i>, <i>PDGFRB</i> OR <i>FGFR1</i>		ACUTE MYELOID LEUKAEMIA (AML) AND RELATED PRECURSOR NEOPLASMS	
Myeloid and lymphoid neoplasms with <i>PDGFRA</i> rearrangement	9965/3	AML with recurrent genetic abnormalities	
Myeloid neoplasms with <i>PDGFRB</i> rearrangement	9966/3	AML with t(8;21)(q22;q22); <i>RUNX1-RUNX1T1</i>	9896/3
Myeloid and lymphoid neoplasms with <i>FGFR1</i> abnormalities	9967/3	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i>	9871/3
		Acute promyelocytic leukaemia with t(15;17)(q22;q12); <i>PML-RARA</i>	9866/3
		AML with t(9;11)(p22;q23); <i>MLLT3-MLL</i>	9897/3
		AML with t(6;9)(p23;q34); <i>DEK-NUP214</i>	9865/3
		AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); <i>RPN1-EV11</i>	9869/3
		AML (megakaryoblastic) with t(1;22)(p13;q13); <i>RBM15-MKL1</i>	9911/3
		AML with mutated <i>NPM1</i>	9861/3
		AML with mutated <i>CEBPA</i>	9861/3
		AML with myelodysplasia-related changes	9895/3
		Therapy-related myeloid neoplasms	9920/3
Myelodysplastic/myeloproliferative neoplasm, unclassifiable	9975/3		
<i>Refractory anaemia with ring sideroblasts associated with marked thrombocytosis</i>	9982/3		

Acute myeloid leukaemia, NOS	9861/3	B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities		Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3	Systemic EBV positive T-cell lymphoproliferative disease of childhood	9724/3
AML with minimal differentiation	9872/3	B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); <i>BCR-ABL1</i>	98	Nodal marginal zone lymphoma	9699/3	Hydroa vacciniforme-like lymphoma	9725/3
AML without maturation	9873/3	B lymphoblastic leukaemia/lymphoma with t(v;11q23); <i>MLL</i> rearranged	98	<i>Paediatric nodal marginal zone lymphoma</i>	9699/3	Adult T-cell leukaemia/lymphoma	9827/3
AML with maturation	9874/3	B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); <i>TEL-AML1</i> (<i>ETV6-RUNX1</i>)	98	Follicular lymphoma	9690/3	Extranodal NK/T cell lymphoma, nasal type	9719/3
Acute myelomonocytic leukaemia	9867/3	B lymphoblastic leukaemia/lymphoma with hyperdiploidy	98	<i>Paediatric follicular lymphoma</i>	9690/3	Enteropathy-associated T-cell lymphoma	9717/3
Acute monoblastic and monocytic leukaemia	9891/3	B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)	98	Primary cutaneous follicle centre lymphoma	9597/3	Hepatosplenic T-cell lymphoma	9716/3
Acute erythroid leukaemia	9840/3	B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); <i>IL3-IGH</i>	98	Mantle cell lymphoma	9673/3	Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Acute megakaryoblastic leukaemia	9910/3	B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); <i>E2A-PBX1</i> (<i>TCF3-PBX1</i>)	98	Diffuse large B-cell lymphoma (DLBCL), NOS	9680/3	Mycosis fungoides	9700/3
Acute basophilic leukaemia	9870/3	T lymphoblastic leukaemia/lymphoma	98	T-cell/histiocyte rich large B-cell lymphoma	9688/3	Sézary syndrome	9701/3
Acute panmyelosis with myelofibrosis	9931/3			Primary DLBCL of the CNS	9680/3	Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	
Myeloid sarcoma	9930/3			Primary cutaneous DLBCL, leg type	9680/3	Lymphomatoid papulosis	9718/1
Myeloid proliferations related to Down syndrome				<i>EBV positive DLBCL of the elderly</i>	9680/3	Primary cutaneous anaplastic large cell lymphoma	9718/3
Transient abnormal myelopoiesis	9898/1			DLBCL associated with chronic inflammation	9680/3	Primary cutaneous gamma-delta T-cell lymphoma	9726/3
Myeloid leukaemia associated with Down syndrome	9898/3			Lymphomatoid granulomatosis	9766/1	<i>Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma</i>	9709/3
Blastic plasmacytoid dendritic cell neoplasm	9727/3			Primary mediastinal (thymic) large B-cell lymphoma	9679/3	<i>Primary cutaneous CD4 positive small/medium T-cell lymphoma</i>	9709/3
ACUTE LEUKAEMIAS OF AMBIGUOUS LINEAGE				Intravascular large B-cell lymphoma	9712/3	Peripheral T-cell lymphoma, NOS	9702/3
Acute undifferentiated leukaemia	9801/3	MATURE B-CELL NEOPLASMS		ALK positive large B-cell lymphoma	9737/3	Angioimmunoblastic T-cell lymphoma	9705/3
Mixed phenotype acute leukaemia with t(9;22)(q34;q11.2); <i>BCR-ABL1</i>	9806/3	Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	98	Plasmablastic lymphoma	9735/3	Anaplastic large cell lymphoma, <i>ALK positive</i>	9714/3
Mixed phenotype acute leukaemia with t(v;11q23); <i>MLL</i> rearranged	9807/3	B-cell prolymphocytic leukaemia	98	Large B-cell lymphoma arising in HHV8- associated multicentric Castleman disease	9738/3	<i>Anaplastic large cell lymphoma, ALK negative</i>	9702/3
Mixed phenotype acute leukaemia, B/myeloid, NOS	9808/3	Splenic marginal zone lymphoma	96	Primary effusion lymphoma	9678/3	HODGKIN LYMPHOMA	
Mixed phenotype acute leukaemia, T/myeloid, NOS	9809/3	Hairy cell leukaemia	99	Burkitt lymphoma	9687/3	Nodular lymphocyte predominant Hodgkin lymphoma	9659/3
<i>Natural killer (NK) cell lymphoblastic leukaemia/lymphoma</i>		<i>Splenic B-cell lymphoma/leukaemia, unclassifiable</i>	95	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma	9680/3	Classical Hodgkin lymphoma	9650/3
PRECURSOR LYMPHOID NEOPLASMS		<i>Splenic diffuse red pulp small B-cell lymphoma</i>	95	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma	9596/3	Nodular sclerosis classical Hodgkin lymphoma	9663/3
B lymphoblastic leukaemia/lymphoma		<i>Hairy cell leukaemia-variant</i>	95	MATURE T-CELL AND NK-CELL NEOPLASMS		Lymphocyte-rich classical Hodgkin lymphoma	9651/3
B lymphoblastic leukaemia/lymphoma, NOS	9811/3	Lymphoplasmacytic lymphoma	96	T-cell prolymphocytic leukaemia	9834/3	Mixed cellularity classical Hodgkin lymphoma	9652/3
		Waldenström macroglobulinemia	97	<i>Chronic lymphoproliferative disorder of NK-cells</i>	9831/3	Lymphocyte-depleted classical Hodgkin lymphoma	9653/3
		Heavy chain diseases	97	Aggressive NK cell leukaemia	9948/3		
		Alpha heavy chain disease	97				
		Gamma heavy chain disease	97				
		Mu heavy chain disease	97				
		Plasma cell myeloma	97				
		Solitary plasmacytoma of bone	97				
		Extrasosseous plasmacytoma	97				

**HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS**

Histiocytic sarcoma	9755/3
Langerhans cell histiocytosis	9751/3
Langerhans cell sarcoma	9756/3
Interdigitating dendritic cell sarcoma	9757/3
Follicular dendritic cell sarcoma	9758/3
Fibroblastic reticular cell tumour	9759/3
Indeterminate dendritic cell tumour	9757/3
Disseminated juvenile xanthogranuloma	

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

Early lesions

Plasmacytic hyperplasia	9971/1
Infectious mononucleosis-like PTLN	9971/1
Polymorphic PTLN	9971/3
Monomorphic PTLN (B- and T/NK-cell types)*	
Classical Hodgkin lymphoma type PTLN*	

NOS, not otherwise specified.

The italicized numbers are provisional codes for the 4th edition of ICD-O. While they are expected to be incorporated in the next ICD-O edition, they currently remain subject to changes.

The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

*These lesions are classified according to the leukaemia or lymphoma to which they correspond, and are assigned the respective ICD-O code.



ANNEXE #2: Establishment of a Reference platform for HematoPathological review

Current situation and Rationale for the establishment of a reference platform for diagnostic review:

Hematopathology, and specifically the diagnosis of Lymphoma, is becoming more and more complex due to the continuous update in lymphoma classification and the need for integration of the morphology with prognostic biomarkers and molecular tests. As this is the case in other organ systems, it becomes more and more difficult for general pathologists to stay updated with all these new findings.

As treatment options fully rely on histopathological diagnosis ('no meat, no treat'), this calls for the establishment of a reference platform for Hematopathology consisting of a group of pathologists with an expertise in hematopathology. The choice for therapeutic agents are more and more personalized depending on the lymphoma subtype and the expression of predictive biomarkers. Suboptimal therapy regimens based upon an incomplete or wrong diagnosis are ineffective and very expensive.

At this moment all pathology labs in Belgium are allowed to make the diagnosis of lymphoma, without systematic revision of the quality of diagnosis or the quality of the immunohistochemical or molecular tests. There is neither the practice of standardized reporting, nor a consensus of which prognostic biomarkers should be reported. This makes comparing diagnoses between different labs very difficult. Another problem is that for a center that has no systematic load of lymphoma cases it is not cost-effective to have all necessary antibodies or molecular techniques available.

Second opinions/revisions of diagnosis are most frequently done in current practice when patients are referred between different centers for treatment or between colleagues when in doubt. There is no RIZIV/INAMI financing available for this kind of revision.

We propose that one national reference platform is established consisting of an independent technical unit on the one hand and a panel of experts in hematopathology (max 10) for systematic central review of all cases on the other hand. Both technical aspects and central review and reporting need to be standardized.

Ideally, an independent technical unit is responsible for the registration of cases, preparation of H&E slides, predefined panels of immunohistochemical stainings, in situ hybridization, scanning of slides, distribution of scanned slides to the reference pathologists, database management and archiving of reviewed cases. The preparation of slides and the immunohistochemical procedures are done according to validated protocols in uniform and standardized conditions.

All lymphoma cases are anonymized and distributed randomly and in a digital fashion to one of the reference pathologists, evenly distributed on a yearly basis between the different reference pathologists. They review and sign out cases on a daily basis. Cases on which there is a disagreement and difficult cases are sent to other experts (national or international if necessary) and can be discussed in interexpert meetings. The review is done according to standardized protocols that are established by the group of reference pathologists. Feedback will be provided to the referring pathologist to improve primary diagnostics. This will improve quality of diagnosis and eventually reduce the costs for the Health Care System.

After revision of diagnosis, patients can be referred for treatment to the original regional center, or to a more specialized (academic) center.



Requirements:

- Development of a financing system for the national technical unit (reference laboratory)
- Development of a financing system for expert panel revisions and interexpert meetings.
- Development of a digital pathology platform for interexpert consultation. Supporting the datamanagement for the generation of database and providing digital storage capacity.

Future Role for any laboratory in lymphoma diagnostics:

- Preparation of tissue blocks.
- Initial review of slides and pathological report to clinician.
- If biopsy suspicious for lymphoma, immediate transfer of tissue blocks (FFPE/frozen) to the technical unit of the reference platform

Future role for the Reference platform in lymphoma diagnostics:

- + Setup of guidelines for diagnosis, reporting (IHC stainings, prognostic biomarkers) of Lymphoma cases.
- + Daily diagnosis (fine tuning/Revision) of all lymphoma cases sent by all Laboratories.
- + Interexpert second review of unusual cases (preferably using telepathology): once-twice monthly
- + Improving diagnostic quality by inter-expert discussion and feedback to referring pathologists
- + Setup of integrated Lymphoma Database/Registry (incl pathology, cytogenetics and molecular analysis) cfr GELA

Selection Procedure for Hematopathology Platform experts (max 10):

Requirements for central technical unit

1. Required facilities and equipment
 - o Independent laboratory (not connected to an existing hospital/ general histopathology lab)
 - o Fully equipped laboratory for Histopathology, with access to all necessary antibodies for IHC (subtyping and prognostic biomarkers) and ISH
 - o Fully equipped laboratory for Molecular Pathology, including PCR, EBER ISH
 - o Facilities for Interexpert Consultation : Multiheaded microscopes; Digital Pathology Platform for tele-expertise and shared repository of cases
 - o (Collaboration with a reference laboratory for Human Genetics for FISH, karyotyping)



2. Quality Assurance

- o Accreditation By “Commission d'Agréation pour les Laboratoires d'Anatomie Pathologique”/ “Erkenningscommissie Pathologische Anatomie”
- o BELAC accreditation of Cytogenetics and Molecular Tests
- o Exhaustive and reliable information sent to Cancer Registry
- o Compliance with existing guidelines and documentation of deviations from guidelines
- o Involvement in quality initiatives (e.g. benchmarking, participation in ringtesting)

Requirements for reference pathologist:

Any pathologist (both academic and regional) can apply for participation in the review panel.

Selection by Commission of peers, based upon the requirement criteria below.

1. General requirements:

- o M.D.
- o Specialist in Surgical Pathology, with Special Training in Hematopathology (based upon fellowships, courses, research experience, publication records, ...)
- o Minimal 3 years of Experience in Hematopathology
- o Participation in Multidisciplinary management, incl MOC

2. Research and other scientific activities

- o Involvement in translational studies (optional: agreements to be made between the reference pathologists)
- o Publications in peer-reviewed journals, grants, ... (optional: agreements to be made between the reference pathologists)
- o Link with a tumour bank (optional)
- o Setup of clinicopathological database
- o Development of clinical practice guidelines for diagnosis and reporting

3. Patient centred care

- o SOP for throughput times for primary diagnosis and revision/second opinion: 7-10 working days
- o Agreements concerning the Continuity of care (between the central technical unit and referring pathologist, between referring pathologist and expert pathologist and between the Reference pathologists and the central technical unit)
- o National and international networking with other Pathology Reference Centres (appropriate arrangements for referrals within Belgium and from/to other EU countries if applicable)