Demystifying the complexity of lymphoma classification

Lymphoma classification according to WHO

The term 'lymphoma' collectively refers to a group of cancers that affect lymphocytes, histocytes and cells derived from lymphoid tissues, at any stage of development.[1]

Recent advances in sequencing techniques have unearthed the genetic landscape of lymphocytic neoplasms and have expanded the heterogeneity between and within lymphoma types.[2] Given that diagnostic testing is not universally available, **classification helps to differentiate lymphoma types and subtypes, ensuring accurate diagnosis and guidance for treatment.[3]**

WHO applies a hierarchal classification to organise lymphoma. Further specificity is assessed by evaluating cell morphology, immunophenotypes, genetic and clinical features, as well as site of presentation and cell derivative. **Each lymphoma type is classified on criteria considered essential and desirable for accurate diagnosis.[3]**

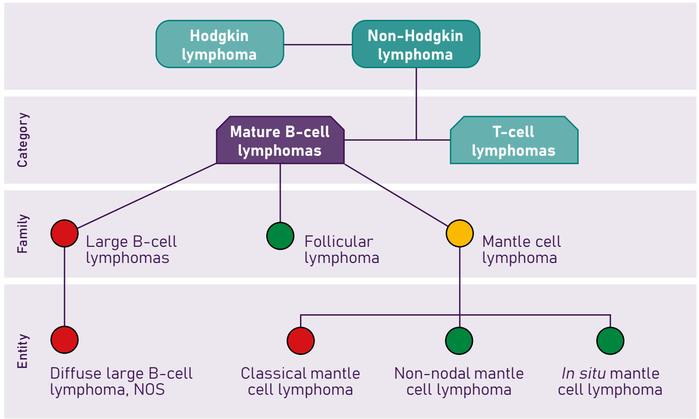
Comparison of WHO and ICC 2022 classifications of mature B-cell neoplasms

Since the 4th WHO edition in 2017, significant scientific and clinical advances have been made in the field of lymphomas, contributing to the revised classification of entities and the identification of new entities. This process has resulted in two recent classifying proposals of mature B-cell neoplasms: ICC and the 5th edition of WHO classification.[3] **Many changes will not have a major clinical impact as long as communication is clear.[8–10]**

WHO 4th edition	WHO 5th edition	ICC 2022
Testicular follicular lymphoma	Not considered an entity	Testicular follicular lymphoma (distinct entity)
Burkitt lymphoma	Burkitt lymphoma (distinguishing EBV+ and EBV–)	Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration (provisional entity)	High-grade B-cell lymphoma with 11q aberrations	Large B-cell lymphoma with 11q aberration (provisional entity)
Nodular lymphocyte-predominant Hodgkin lymphoma (not included in this category; see Hodgkin lymphoma)	Nodular lymphocyte-predominant Hodgkin lymphoma (not included in this category; see Hodgkin lymphoma)	Nodular lymphocyte-predominant B-cell lymphoma
High-grade B-cell lymphoma with dual rearrangements of MYC and BCL2 and/or BCL6	DLBCL/high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6	High-grade B-cell lymphoma with MYC and BCL2/BCL6 rearrangement
Follicular lymphoma (1–2, 3A, 3B)	Classic follicular lymphoma (grade 1–2 and 3A) Follicular large B-cell lymphoma (grade 3B)	Follicular lymphoma (with grading 1–2, 3A, 3B)

WHO classification of mature B-cell lymphomas

Mature B-cell neoplasms represent 80% of NHLs.[2] Among the mature B-cell lineage, MCL and LBCL are both familial members.[3–5]



KEY

- High-grade lymphomas
- Intermediate
- Low-grade lymphomas

DLBCL is the most common NHL, representing 30–40% of cases.[6] WHO classifies DLBCL NOS into the new LBCL family, but recognises only 17 LBCL types due to diversity among diagnostic features.[3]

WHO recommends the GCB/ABC distinction of DLBCL NOS following gene expression profiles but acknowledges clinical impact is limited.

Family of FL encompasses FL, ISFN, paediatric-type FL and duodenal-type FL.

There have been no significant updates on the latter three entitities in WHO 5th edition, however the entity of FL has undergone significant revision.

The vast majority of FL (85%) have at least in part a follicular growth pattern, are composed of centrocytes and centroblasts and harbour the t(14;18)(q32;q21) translocation associated with IGH::BCL2 fusion; these are now termed cFL and set apart from two related subtypes/groups, FLBL and uFL.[3]

MCL is hallmarked by the translocation of IGH-CCND1.[4] WHO classifies MCL into three types: *in situ* (ISMCN), non-nodal (nnMCL) and classical (cMCL).

cMCL is an aggressive type, affecting lymph nodes and extra-nodal sites.

nnMCL is characterised by the involvement of blood, bone marrow and spleen, with little or no lymphadenopathy.

ISMCN is a rare type that presents as B cells with IGH-CCND1 fusion in non-expanded mantle zones of lymph nodes.[7]

Navigating the updated WHO classification of HGBL types[3,11]

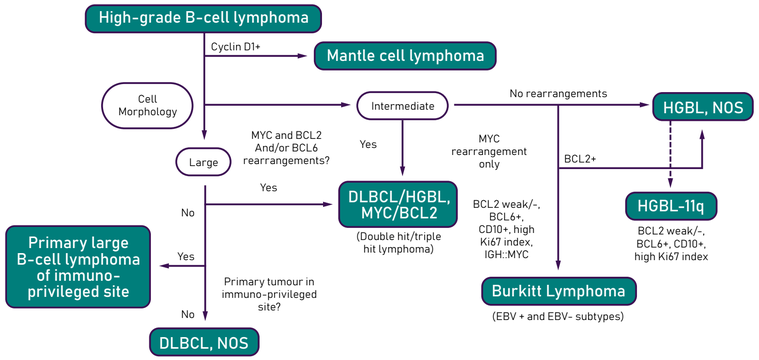
HGBL can be accurately differentiated from other lymphoma types by assessing morphology, immunophenotypes and genetic profiles.

Immunohistochemistry of cyclin-D1 and SOX-11 or FISH for IGH-CCND1 translocation can identify MCL.

FISH for MYC and BCL2/6 mutations are used to classify double or triple hit lymphoma and differentiates DLBCL NOS, Burkitt lymphoma and HGBL NOS.

DLBCL/HGBL with MYC and BCL2 are recognised as double hit lymphoma. Aggressive lymphoma types that are negative with MYC rearrangements are classified as HGBL NOS. HGBL-11q being recognised as a new entity takes into account overlapping features with Burkitt lymphoma in the absence of MYC rearrangements.

DLBCL represents lymphomas that lack criteria-defining specific types. DLBCL arising from primary tumours of the CNS, vitreoretinal compartment and testis are now grouped into primary large B-cell lymphomas of immune-privileged sites.



Summary

- Lymphomas represent a broad range of disease types with differing morphological, genetic and clinical features
- WHO classifies lymphomas by category, family/class, entity/type and subtype, taking into account essential and desirable criteria needed for accurate diagnosis
- WHO have updated their classification to reflect improved scientific and clinical understanding of lymphoid tumours
- Classification of lymphomas ensures universal and accurate diagnosis for patients. New naming conventions and entities must be communicated and documented clearly

ABC, activated B-cell; BCL2/6, B-cell lymphoma 2/6; BCR, B-cell receptor; CCND1, cyclin D1; CD, cluster of differentiation; cFL, classic follicular lymphoma; CHL, classical Hodgkin lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FISH, fluorescence in situ hybridisation; FL, follicular lymphoma; FLBL, follicular large B-cell lymphoma; GCB, germinal centre B cell; HL, Hodgkin lymphoma; HGBL, high-grade B-cell lymphoma; ICC, International Consensus Classification; IGH, immunoglobulin heavy locus; ISFN, in situ follicular B-cell neoplasm; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MYC, MYC proto-oncogene; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; PRDM1, PR domain zinc finger protein 1; SOX-11, sex determining region Y-box 11; Tdt, terminal deoxynucleotidyl transferase; uFL, follicular lymphoma with uncommon features; WHO, World Health Organization

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