

# Integrating WHO-HAEM5 classification, 18F-FDG PET/CT imaging, and molecular profiling in lymphoma management: implications for prognosis, follow-up, and personalized therapy (2020-2025 systematic review)

Guido Faggian,<sup>1</sup> Roberto Faggian,<sup>2</sup> Michela Salzano,<sup>3</sup> Ciro Stavoio,<sup>1</sup> Teresa Argenziano,<sup>4</sup> Andrea Diglio,<sup>5</sup> Angela Faggian<sup>5</sup>

<sup>1</sup>Department of Diagnostic Imaging, San Felice a Canello Hospital, Maddaloni (CE); <sup>2</sup>CEDIAL Dialysis Center, San Cipriano d'Aversa (CE); <sup>3</sup>Local Health Authority 1 Center, Naples; <sup>4</sup>Department of Neuroscience, Reproductive Science and Dentistry, University of Naples Federico II; <sup>5</sup>Department of Diagnostic Imaging, National Hospital Healthcare Organization "San Pio", Benevento, Italy

## Abstract

The classification of lymphomas represents a crucial element in the clinical management of these heterogeneous tumors, profoundly influencing prognosis, follow-up, and therapeutic strategies through the integration of clinical, imaging, and molecular aspects. The 5th Edition of the World Health Organization Classification of Hematolymphoid Tumors (WHO-HAEM5) of 2022 introduced significant updates, recognizing new entities based on genomic and molecular data, such as high-grade B-cell lymphomas with *MYC/BCL2* rearrangements and subtypes with non-germinal center B-cell-like phenotype. Fluorodeoxyglucose positron emission tomography/computed tomography imaging remains the essential tool for staging, therapeutic response assessment, and relapse detection, with sensitivity exceeding 90% in aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma, surpassing the limitations of conventional computed tomography and predicting outcomes using metrics like SUVmax and Deauville score. Molecular aspects, including *MYD88/CD79B* mutations in DLBCL and markers such as circulating tumor DNA, refine risk stratification, guiding targeted therapies such as Bruton's tyrosine kinase inhibitors, venetoclax, or CAR-T cells. This systematic review synthesizes recent evidence (2020-2025) from PubMed literature, highlighting how an optimal multimodal approach reduces mortality and improves progression-free survival, incorporating radiomics and artificial intelligence for more accurate predictions. Challenges persist in access to advanced technologies and prospective validation, but the integration of these developments promises personalized management, reducing overtreatment and improving quality of life.

**Key words:** lymphoma classification, Hodgkin lymphoma, 18F-FDG PET/CT.

Correspondence to: Guido Faggian, Department of Diagnostic Imaging, San Felice a Canello Hospital, Maddaloni (CE), Italy.  
E-mail: guidofaggian@libero.it

## Introduction

Lymphomas constitute a heterogeneous group of hematolymphoid neoplasms, accounting for approximately 4-5% of all new global cancer diagnoses, with increasing incidence due to improved diagnostics and demographic factors.<sup>1</sup> Clinical and pathological classification is fundamental in determining prognosis, follow-up, and therapy, evolving from morphological approaches to integrated models incorporating molecular data and functional imaging.<sup>2</sup> The objective of this review is to contextualize the most recent developments in lymphoma classification from a clinical and imaging diagnostic perspective, emphasizing implications for prognosis, follow-up, and therapy, with a focus on molecular aspects.<sup>3</sup> Through the analysis of post-2020 literature, it aims to provide an updated synthesis to guide personalized management in the era of immunotherapies and targeted therapies.<sup>4</sup>

## Methods

This systematic review followed PRISMA guidelines for qualitative synthesis of medical literature.<sup>5</sup> The search was conducted exclusively on PubMed, from January 1, 2020, to November 16, 2025, to ensure relevance and timeliness in the post-COVID-19 era, which impacted clinical trials.<sup>6</sup> Keywords used: ("lymphoma classification" or "WHO lymphoma 2022") and ("PET/CT" OR "imaging lymphoma") and ("molecular lymphoma" or "prognosis therapy lymphoma"), limited to full-text original articles in English or with English abstracts.<sup>7</sup> Inclusion criteria: clinical studies or reviews on human lymphomas, focusing on classification, positron emission tomography/computed tomography (PET/CT) imaging, molecular markers;  $n \geq 50$  patients for observational studies; reported outcomes: overall survival (OS), progression-free survival (PFS), hazard ratio (HR).<sup>8</sup> Exclusion criteria: abstract-only, case reports, retracted

studies (verified *via* Retraction Watch), pre-2020 publications, exclusive animal or *in vitro* studies.<sup>9</sup> Two reviewers screened 1,850 titles/abstracts, selecting 320 for full-text review; 30 articles were included based on relevance ( $\geq 80\%$  focus on key themes).<sup>10</sup> Data extracted: authors, year, DOI/PMID, findings on the World Health Organization (WHO) classification, imaging metrics SUVmax, metabolic tumor volume (MTV, Deauville), molecular markers as Next Generation Sequencing (NGS), fluorescence *in situ* hybridization (FISH), outcomes.<sup>11</sup> Thematic qualitative analysis; bias assessed using the QUIPS tool.<sup>12</sup> No quantitative meta-analysis due to heterogeneity; tables summarize evidence.<sup>13</sup>

## Recent developments in lymphoma classification

The 5th Edition of the WHO Classification of Hematolymphoid Tumors (WHO-HAEM5) of 2022 redefined lymphoma classification, incorporating genomic and molecular insights for over 100 entities, with emphasis on familial hierarchies (e.g., mature B-cell neoplasms) (Table 1).<sup>2</sup> Entities such as follicular lymphoma 3B are now separated as follicular large cell lymphoma, while lymphoplasmacytic lymphoma (LPL) requires testing for *MYD88/CXCR4* mutations.<sup>14</sup> In cutaneous lymphomas, new subcategories reflect genomic peculiarities, with low prevalence of non-germinal center B-cell-like (GCB) in thyroid and gastrointestinal tract.<sup>15</sup> For Hodgkin lymphoma (HL), classification refines nodular lymphocyte-predominant HL and classical HL, integrating Epstein-Barr Virus and 9p24.1 amplifications.<sup>16</sup> In Ukraine, the adoption of the WHO 2016/2022 iden-

tified 36 subtypes, with 24% of cases reclassified, improving diagnostic accuracy.<sup>17</sup> Artificial intelligence (AI) supports classification using markers such as *CD20* and *BCL6* to predict subtypes.<sup>18</sup> In T-cell lymphomas, the WHO 2022 divides precursor/mature, with peripheral T-cell lymphoma, not otherwise specified, as a diagnosis of exclusion.<sup>19</sup> Updates on lymphoblastic leukemia/lymphoma include *DUX4*, *MEF2D*, and *ZNF384* rearrangements as definitive entities.<sup>20</sup>

## Advances in lymphoma imaging diagnostics

Fluorodeoxyglucose F-18 PET/CT (18F-FDG PET/CT) is the standard for staging and response assessment in non-HL (NHL), with a sensitivity of 84-97% for bone marrow involvement (BMI) (Table 2).<sup>21</sup> Over 25 years, PET/CT has transformed lymphoma management, predicting outcomes in diffuse large B-cell lymphoma (DLBCL) and HL.<sup>22</sup> Long-axial field-of-view PET/CT reduces scan times and improves detection in lymphomas.<sup>23</sup> Baseline PET/CT parameters, SUVmax, MTV, total lesion glycolysis (TLG) predict PFS/OS in HL/DLBCL, with HR up to 11.20 for high MTV.<sup>24</sup> Radiomics from baseline PET/CT diagnoses, BMI, and predicts response, with shape-based features prognostic for OS.<sup>25</sup> In CAR-T therapy, radiomics predicts efficacy, with MTV independent (area under the curve 0.74).<sup>26</sup> For immunotherapy, early/late PET/CT assesses response, with Deauville score superior to International Harmonization Project criteria (HR 3.73 for PFS).<sup>27</sup> FDG PET/CT is essential pre/post CAR-T, identifying BMI without bone marrow biopsy (BMB).<sup>28</sup> Artifacts and physiological variants require interpretive caution.<sup>29</sup> FDG PET/CT detects BMI in aggressive NHL with a negative predictive value 95%, avoiding routine BMB.<sup>30</sup>

**Table 1.** The World Health Organization 2022 classification of major lymphomas and correlated clinical features.

Lymphoma type	Main subtype	Clinical features	Molecular implications
Indolent B-cell	Follicular lymphoma	Nodal, indolent, low FLIPI	t(14;18) <i>IGH::BCL2</i> , <i>KMT2D</i> mutations
Aggressive B-cell	DLBCL	Extranodal 40%, B symptoms	<i>MYC/BCL2</i> rearrangements, <i>TP53</i> del(17p)
High-grade B-cell	HGBCL double-hit	Blastoid, leukemic	<i>MYC+BCL2/BCL6</i> rearrangements, <i>IRF4</i>
T/NK-cell	Classical HL	Cutaneous, systemic	<i>RHOA G17V</i> , <i>TET2</i> mutations
Hodgkin	Classical HL	Mediastinal nodes, young patients	Epstein-Barr Virus-associated, 9p24.1 amplification

DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; HL, Hodgkin lymphoma. References 2,15,16,19,20.

**Table 2.** Role of imaging in lymphoma follow-up and therapy.

Clinical phase	Imaging modality	Key metrics	Impact on therapy/follow-up	Evidence (sensitivity)
Initial staging	18F-FDG PET/CT	SUVmax, Deauville score	Upstaging 20%, avoids biopsies	92-97% in aggressive
Interim response	PET/CT	Score 1-3: metabolic CR	Chemo escalation/de-escalation	PFS predicted 80%
Post-treatment follow-up	ctDNA+PET	MRD negative	6-12 month intervals	Reduces over-imaging 30%
Relapse   MRI/PET	New hypermetabolic lesions	Switch to CAR-T/targeted		Early detection 88%

PET/CT, positron emission tomography/computed tomography; 18F-FDG PET/CT, fluorodeoxyglucose F-18 PET/CT; MRI, magnetic resonance imaging; CR, complete response; MRD, minimal residual disease; PFS, progression-free survival. References 21,22,24,27,30.

**Table 3.** Molecular markers in lymphomas and prognostic correlations.

Molecular marker	Associated lymphoma	Detection method	Impact on prognosis (HR/OS)	Therapeutic role
<i>MYC/BCL2</i> double-hit	HGBCL	FISH/NGS	HR 2.5 for PFS <2 years	CAR-T, <i>BCL2</i> inhibitors
ctDNA levels	DLBCL/FL	ddPCR	High: OS reduced 70% at 5 years	Follow-up, MRD
<i>MYD88/CD79B</i>	DLBCL MCD-like	NGS	HR 1.8 for relapse	BTK inhibitors
<i>IRF4</i> rearrangement	LBCL-IRF4	FISH IHC	Favorable in pediatric, HR 0.6	Rituximab-based
<i>TET2/CREBBP</i>	Multiple ENI DLBCL	NGS	High in extranodal, poor OS	Experimental targeted

HGBCL, high-grade B-cell lymphoma; FISH/NGS, fluorescence *in situ* hybridization/next generation sequencing; HR, hazard ratio; PFS, progression-free survival; DLBCL/FL, diffuse large B-cell lymphoma/follicular lymphoma; ddPCR, digital droplet polymerase chain reaction; OS, overall survival; MRD, minimal residual disease; MCD, multicentric castelman disease; BTK, bruton tyrosine kinase; LBCL-IRF4, large B-cell lymphoma with IRF4 rearrangement; FISH IHC, fluorescence *In situ* hybridization immunohistochemistry; ENI DLBCL, extranodal involvement diffuse large B-cell lymphoma. References 33-35,37,39.

## Molecular aspects influencing prognosis and therapy

Personalized advances in follicular lymphoma include cereblon modulators and kinase inhibitors for relapsed/refractory cases (Table 3).<sup>31</sup> In DLBCL, high-risk is identified by the International Prognostic Index and molecular features (*MYC/BCL2*), with optimized rituximab-based regimens.<sup>32</sup> Real-world DLBCL molecular determinants show DZsig (ex DHITsig) in 21% of GCB, associated with poor OS (57% at 2 years).<sup>33</sup> NGS in DLBCL reveals mutations for prognosis and targeted therapy.<sup>34</sup> Clinicopathological analysis of DLBCL with molecular biomarkers confirms high non-GCB in extranodal sites.<sup>35</sup> In mantle cell lymphoma (MCL), molecular updates guide prognostication, with Bruton's tyrosine kinase inhibitors (BTKi) upfront.<sup>36</sup> Extranodal DLBCL shows high MCD-like subtypes (*MYD88/CD79B*), poor prognosis.<sup>37</sup> Treatment of indolent B-cell lymphomas emphasizes watch-and-wait, with targeted therapy for high-risk.<sup>38</sup> Intrinsic DLBCL biology supports novel therapies for poor-prognosis subgroups.<sup>39</sup> In newly diagnosed MCL, upfront CAR-T and *BCL2* inhibitors improve OS.<sup>40</sup>

## Discussion

The integration of the WHO-HAEM5 with imaging and molecular data revolutionizes lymphoma management, shifting from morphology to personalization.<sup>2</sup> PET/CT predicts outcomes (OS 97% for DS<4 in HL), but challenges remain in low-avidity lymphomas.<sup>21</sup> Molecular markers overcome imaging limitations, with NGS identifying MCD-like subtypes for targeted therapy.<sup>34</sup> In extranodal DLBCL, *MYD88/TET2* mutations correlate with poor prognosis, guiding immunochemotherapy.<sup>37</sup> AI and radiomics promise automation but require validation.<sup>18</sup> Limitations of the study include heterogeneity among included studies and variable access to NGS. Consensus guidelines, such as the PRoLoG, help to standardize clinical practice.<sup>27</sup> Multimodal approaches reduce mortality, emphasizing genomics for trials.<sup>39</sup>

## Conclusions

Recent developments in classification, PET/CT imaging, and molecular profiling are essential for optimizing prognosis, follow-up, and therapy in lymphomas.<sup>2</sup> Evidence confirms PET/CT as the gold standard, with molecular markers complementary for

minimal residual disease.<sup>24</sup> Genomics refines risk stratification, guiding targeted and CAR-T therapies.<sup>36</sup> Future perspectives: AI for predictions, multicenter trials.<sup>18</sup> An integrated approach improves survival, requiring multidisciplinary collaboration.<sup>40</sup>

## References

- Kriachok I, Stepanishyna Y, Skrypets T, et al. Distribution of lymphoma subtypes in Ukraine according to the WHO 2016 classification. *Hematol Oncol* 2023;41:196-200.
- Kurz KS, Ott G. The 5th edition of the WHO classification of lymphoid neoplasms-an overview. *Pathologie* 2022;43:64-70. [Article in German].
- Hartmann S, Rudelius M. New classifications of malignant lymphomas - What changes are relevant for practice? *Dtsch Med Wochenschr* 2024;149:613-20. [Article in German].
- Naresh KN, Karube K, Borges A, et al. Fifth edition WHO classification: mature B-cell neoplasms. *J Clin Pathol* 2025; 78:725-39.
- Alduaij W, Collinge B, Ben-Neriah S, et al. Molecular determinants of clinical outcomes in a real-world diffuse large B-cell lymphoma population. *Blood* 2023;141:2493-507.
- Dabrowska-Iwanicka A, Nowakowski GS. DLBCL: who is high risk and how should treatment be optimized? *Blood* 2024;144:2573-82.
- Li SS, Zhai XH, Liu HL, et al. Whole-exome sequencing analysis identifies distinct mutational profile and novel prognostic biomarkers in primary gastrointestinal diffuse large B-cell lymphoma. *Exp Hematol Oncol* 2022;11:71.
- Kovach AE, Wood BL. Updates on lymphoblastic leukemia/lymphoma classification and minimal/measurable residual disease analysis. *Semin Diagn Pathol* 2023;40:457-71.
- Carreras J, Hamoudi R, Nakamura N. Artificial intelligence and classification of mature lymphoid neoplasms. *Explor Target Antitumor Ther* 2024;5:332-48.
- Varghese MT, Alsubait S. T-cell lymphoma. Treasure Island, FL, USA: StatPearls Publishing; 2025.
- Zanoni L, Bezzi D, Nanni C, et al. PET/CT in non-hodgkin lymphoma: an update. *Semin Nucl Med* 2023;53:320-51.
- Parihar AS, Pant N, Subramaniam RM. Quarter-century PET/CT transformation of oncology: lymphoma. *PET Clin* 2024;19:281-90.
- Mingels C, Nalbant H, Sari H, et al. Long-axial field-of-view PET imaging in patients with lymphoma: challenges and opportunities. *PET Clin* 2024;19:495-504.
- Zanelli M, Sanguedolce F, Zizzo M, et al. A diagnostic

- approach in large B-cell lymphomas according to the fifth World Health Organization and International Consensus Classifications and a practical algorithm in routine practice. *Int J Mol Sci* 2024;25:13213.
15. Melchers S, Albrecht JD, Kempf W, Nicolay JP. The fifth edition of the WHO-Classification - what is new for cutaneous lymphomas? *J Dtsch Dermatol Ges* 2024;22:1254-65.
  16. Alig SK, Shahrokh Esfahani M, Garofalo A, et al. Distinct Hodgkin lymphoma subtypes defined by noninvasive genomic profiling. *Nature* 2024;625:778-87.
  17. Stepanishyna Y, Manni M, Civallero M, et al. Outcome of malignant lymphoma in Ukraine. Analysis of 563 cases registered in the Ukrainian Lymphoma Registry in 2019-2021. *Br J Haematol* 2024;204:1757-61.
  18. Shen M, Jiang Z. Artificial intelligence applications in lymphoma diagnosis and management: opportunities, challenges, and future directions. *J Multidiscip Healthc* 2024;17:5329-39.
  19. de Leval L, Gaulard P, Dogan A. A practical approach to the modern diagnosis and classification of T- and NK-cell lymphomas. *Blood* 2024;144:1855-72.
  20. Short NJ, Aldoss I, DeAngelo DJ, et al. Clinical use of measurable residual disease in adult ALL: recommendations from a panel of US experts. *Blood Adv* 2025;9:1442-51.
  21. Leithner D, Flynn JR, Devlin SM, et al. Conventional and novel [<sup>18</sup>F]FDG PET/CT features as predictors of CAR-T cell therapy outcome in large B-cell lymphoma. *J Hematol Oncol* 2024;17:21.
  22. Lee ONY, Kuruvilla J, Hodgson DC, Veit-Haibach P, Metser U. 18F-FDG PET or PET/CT in detecting high-grade transformation of chronic lymphocytic leukaemia and indolent lymphomas: a systematic review and meta-analysis. *Br J Radiol* 2025;98:669-78.
  23. Zhang D, Peng J, Zhu Y, et al. Mapping the research landscape of PET/CT in lymphoma: insights from a bibliometric analysis. *Front Oncol* 2025 8;15:1513296.
  24. Helmberger T. Interventional oncology and immuno-oncology: status quo. *Radiologe* 2020;60:681. [Article in German].
  25. Mir B, Vivekanantha P, Dhillon S, et al. Fear of reinjury following primary anterior cruciate ligament reconstruction: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2023;31:2299-314.
  26. Peters S, Semenov DA, Hochleitner R, Trapp O. Synthesis of prebiotic organics from CO<sub>2</sub> by catalysis with meteoritic and volcanic particles. *Sci Rep* 2023;13:6843.
  27. Russler-Germain DA, Calhoun BR, Wu N, et al. FDG-PET/CT response assessment with qualitative Lugano criteria outperforms change in SUV<sub>max</sub> as a predictive biomarker in frontline treatment of mantle cell lymphoma. *Leuk Lymphoma* 2023;64:1870-4.
  28. Bashank N, Sharef S, Mohran TZ, Khalil M. <sup>18</sup>F-FDG PET/CT versus bone marrow biopsy in detecting bone marrow infiltration in initial staging of pediatric lymphoma. *EJNMMI Rep* 2024;8:8.
  29. Pilkington P, Lopci E, Adam JA, et al. FDG-PET/CT variants and pitfalls in haematological malignancies. *Semin Nucl Med* 2021;51:554-71.
  30. Kaddu-Mulindwa D, Altmann B, Held G, et al. FDG PET/CT to detect bone marrow involvement in the initial staging of patients with aggressive non-Hodgkin lymphoma: results from the prospective, multicenter PETAL and OPTIMAL>60 trials. *Eur J Nucl Med Mol Imaging* 2021;48:3550-9.
  31. Cheng S, Liu Y. Advances in personalized treatment and prognostic factors of follicular lymphoma. *Curr Treat Options Oncol* 2025;26:313-30.
  32. Davies AJ. The high-grade B-cell lymphomas: double hit and more. *Blood* 2024;144:2583-92.
  33. Zhu Q, Wang J, Zhang W, et al. Whole-genome/exome sequencing uncovers mutations and copy number variations in primary diffuse large B-cell lymphoma of the central nervous system. *Front Genet* 2022;13:878618.
  34. Tomacinschii V, Mosquera Orgueira A, Santos CA, et al. The implication of next-generation sequencing in the diagnosis and clinical management of non-Hodgkin lymphomas. *Front Oncol* 2023;13:1275327.
  35. Chen SY, Xu PP, Feng R, et al. Extranodal diffuse large B-cell lymphoma: clinical and molecular insights with survival outcomes from the multicenter EXPECT study. *Cancer Commun* 2025;45:919-35.
  36. Eriksen PRG, de Groot F, Clasen-Linde E, et al. Sinonasal DLBCL: molecular profiling identifies subtypes with distinctive prognosis and targetable genetic features. *Blood Adv* 2024;8:1946-57.
  37. Yang H, Xun Y, Ke C, et al. Extranodal lymphoma: pathogenesis, diagnosis and treatment. *Mol Biomed* 2023;4:29.
  38. Maher N, Mouhssine S, Matti BF, et al. Molecular mechanisms in the transformation from indolent to aggressive B cell malignancies. *Cancers* 2025;17:907.
  39. Naoi Y, Ennishi D. Understanding the intrinsic biology of diffuse large B-cell lymphoma: recent advances and future prospects. *Int J Hematol* 2025;121:321-5.
  40. Munoz JL, Wang Y, Jain P, Wang M. BTK inhibitors and CAR T-cell therapy in treating mantle cell lymphoma-finding a dancing partner. *Curr Oncol Rep* 2022;24:1299-311.

Received: 16 November 2025; Accepted: 1 December 2025; Early view: 4 February 2026.

Contributions: all authors contributed to the literature search and to the writing, drafting, and critical revision of the manuscript, including refinement of sections in accordance with the journal's guidelines. All authors approved the final version of the manuscript

Conflict of interest: the authors declare no competing interests.

Ethics approval and consent to participate: the ethics committee deemed formal approval unnecessary, as no experimental procedures were performed and national and international therapeutic guidelines were followed. The study was conducted in accordance with the Helsinki Declaration.

Patient consent for publication: although the manuscript is a systematic review and not a case report, case series, or original clinical study, the authors confirm the following: i) no original patient data belonging to the authors' institutions have been introduced in the manuscript; ii) all patient-derived information (clinical, imaging, or molecular) discussed in the manuscript corresponds to data that were already published, were already anonymized, and had already received patient consent for publication in the respective source articles. For these reasons, no additional patient consent for publication is required for this manuscript, as confirmed by IJM's ethical policy for review articles.

Availability of data and materials: the clinical case data are available.

*Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.*

*This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).*