DIFFUSE LARGE B-CELL LYMPHOMA
NATIONAL CLINICAL PRACTICE GUIDELINES

NATIONAL INTEGRATED
CANCER CONTROL PROGRAM

Diffuse Large B-Cell Lymphoma National Clinical Practice Guidelines

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Abbreviations and Acronyms

2D RT	Conventional Radiation Therapy
3D CRT	Three-Dimensional Conformal Radiation Therapy
AGREE	Appraisal of Guidelines for Research and Evaluation
AE	Adverse Event
HCV	Chronic Hepatitis C Virus
CPG	Clinical Practice Guideline
CD	Cluster Differential
CBC	Complete Blood Count
CT	Computed Tomography Scan
COI	Conflict of Interest
CP	Consensus Panel
DFS	Disease-free survival
DLBCL	Diffuse Large B-Cell Lymphoma
DOH	Department of Health (Philippines)
EAMC	East Avenue Medical Center
EBER	Epstein-Barr Encoding Region
EBV	Epstein-Barr Virus
EFS	Event-free survival
ERE	Evidence Review Experts
FISH	Fluorescence In Situ Hybridization
GCB	Germinal Center B-Cell
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GDG	Guideline Development Group
HBSAG	Hepatitis B Surface Antigen Test
IMRT	Intensity Modulated Radiotherapy
iCa	Ionized Calcium
IPI	International Prognostic Index
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NPG	National Practice Guideline
BUN	Blood Urea Nitrogen
NHL	Non-Hodgkin Lymphoma
OS	Overall survival
PICO	Population, Intervention, Comparison, Outcome
PIPOH	Population, Intervention, Professionals, Outcomes, Healthcare setting

PET	Positron Emission Tomography
PFS	Progression-free survival
QoL	Quality of Life
R-CHOP	Rituximab + Cylophosphamide + Hydroxydaunorubicin hydrochloride (Doxorubicin hydrochloride) + Vincristine (Oncovin) + Prednisone
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic-Oxaloacetic Transaminase
TLS	Tumor Lysis Syndrome
WHO	World Health Organization

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The Technical Advisory Group composed of EAMC, DOH, and Philippine Health Insurance Corporation (PhilHealth) representatives serves as the oversight committee ensuring quality and inclusive development of the guideline.

EAMC contracted HPPM as an independent study group to provide highly technical assistance to develop the DLBCL NCPG through a series of consultations and evidence reviews.

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- East Avenue Medical Center (EAMC)
- Philippine Society of Pathologists (PSP)
- Philippine College of Hematology and Transfusion Medicine (PCHTM)
- Philippine College of Radiology (PCR)
- Philippine Society of Medical Oncology (PSMO)
- Philippine Radiation Oncology Society (PROS)
- Lymphoma Philippines

Contributors

The Diffuse Large B-Cell Lymphoma National Clinical Practice Guidelines (DLBCL NCPG) were developed in collaboration with guideline developers and members of various professional societies. All contributors completed the declaration of interest form.

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Dr. Rich King, Dr. Karen Mondragon, Ms. Maria Vanessa Sulit, and Dr. Roger Velasco contributed to the technical assistance on the appraisal of recommendations and guidelines.

Dr. Ian Theodore Cabaluna and Dr. Jeriel de Silos provided systematic reviews and guidance on the implementation, drafted recommendations, and applied their expertise as the technical reviewers and subject matter experts for DLBCL.

The project was only possible with the administrative, coordination, and review services provided by Mr. Teddy Dizon, Ms. Hygeia Grace Agosto, and Ms. Jessica Hernandez.

The CP reviewed the available evidence and developed recommendation statements. The panel included Dr. Maria Claudia Chavez (EAMC), Ms. Alyanna Riel Panlilio (DOH), Dr. Catherine Rosales (PCHTM), Dr. Flordeluna Mesina (PCHTM), Dr. Jomell Julian (PCHTM), Dr. Judy Lee (PCHTM), Dr. Stephen Garcia (PSMO), Dr. Jasmin Igama (PSMO), Dr. Christian Cuaresma (PSMO), Dr. Teresa Sy Ortin (PROS), Dr. Dennis Doromal (PROS), Dr. Rose Lou Marie Agbay (PSP), Dr. Januario Veloso (PSP), Dr. Jonas Santiago (PCR), and Dr. Khristine Pulido-Brillo (PCR).

Executive Summary

Diffuse Large B-Cell Lymphoma (DLBCL) is a type of non-Hodgkin lymphoma that is life-threatening and manageable with the appropriate treatment protocol. To improve standards of care and reduce variations in professional practice, local practice guidelines for this disease will be useful for clinicians, health policy makers, and patients.

The DLBCL National Clinical Practice Guidelines (NCPG) aim to provide evidence-based standards of diagnosis and treatment that meet all the quality requirements stipulated in the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. It includes high-priority questions on the diagnosis and treatment protocol for this disease.

The Guideline Development Group (GDG) employed the ADAPTE process in developing this NCPG. The Technical Advisory Group (TAG) provided the Population, Intervention, Professionals, Outcomes, and Healthcare setting (PIPOH) framework for selecting and framing clinical questions. The Steering Committee used this framework in developing, prioritizing, and rationalizing the practice guideline questions.

The Evidence Review Experts (ERE) conducted evidence-gathering, appraisal, and synthesis to answer the priority practice guideline questions. Finally, the Consensus Panel (CP) scrutinized the summary of evidence and participated in the eDelphi consensus-building process to finalize the recommendation for each practice guideline question.

Diffuse Large-B Cell Lymphoma

The Guideline Development Group used the ADAPTE methodology to generate and finalize the recommendations for DLBCL NCPG, covering diagnosis and clinical management. The ADAPTE process results in the adoption and adaption of recommendations from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Diffuse Large B-Cell Lymphoma and supplemented from The National Institute for Health and Care Excellence (NICE).

Table 1. Diffuse Large B-Cell Lymphoma NCPG Summary

Clinical Questions	Recommendations	SoR	QoE
Diagnosis			
What are the mandatory tests to diagnose and subclassify DLBCL (de novo and transformed cases)?	We recommend excisional biopsy, immunohistochemistry (staining for pan-B cell markers such as *CD19, CD20, CD22 and CD79a*) and conventional karyotyping to diagnose for DLBCL-suspected patients.	Strong	Low
	When the lymph node is not easily accessible for excisional (or incisional) biopsy, we suggest a combination of core biopsy and FNA biopsies, in conjunction with appropriate and available ancillary techniques for the differential diagnosis.	Weak	Low
What tests are needed to determine the extent of DLBCL?	We suggest the following diagnostic work-up to determine the extent of the disease among newly diagnosed DLBCL patients: a. Clinical evaluation (history, physical and neurologic examination); b. Chest/abdomen/pelvic CT scan with contrast of quality diagnostics; c. For patients with neurologic findings on clinical evaluations, lumbar puncture with evaluation of cerebrospinal fluid; d. For patients with high-risk CNS manifestation [including those with greater 1 extra nodal site or certain extra nodal sites (kidney, adrenal gland, testis)] or with neurologic manifestations (re: mass effect), offer head or neck CT scan or MRI with contrast of quality diagnostics; and,	Weak	Low

	e. If CT scan is inconclusive or PET/CT scan is equivocal, offer bone marrow biopsy.		
Treatment and Care			
What essential tests are needed prior to starting treatment and how frequent are these tests monitored during treatment?	We recommend the following pretreatment evaluation among newly diagnosed DLBCL patients: a. Clinical evaluation (*routine*) i. History to identify evidence of comorbidities (heart and renal dysfunction) ii. Physical examination on lymph node-bearing areas (Waldeyer's ring) and size of liver and spleen iii. Neurologic assessment b. Laboratory studies (*routine*) i. Complete blood count with differential count ii. Serum chemistries [electrolytes (i.e., calcium, phosphorous), kidney and liver function tests, uric acid, and lactate dehydrogenase] iii. Hepatitis B surface antigen iv. HIV test among high-risk population c. Imaging (*routine and based on clinical evaluation*) i. Left ventricular ejection fraction assessment through echocardiogram	Strong	Low
What is the role of Tumor Lysis Syndrome (TLS) prophylaxis in DLBCL?	We recommend prophylaxis for tumor lysis syndrome whenever available and/or accessible to patient. The following prophylactic strategies should be considered: a. Allopurinol b. Febuxostat, if intolerant to Allopurinol c. Rasburicase (*if available*), if with the following conditions: i. Patient with urgent need to initiate therapy in a high bulk patient	Strong	Low

	ii. Situations where adequate hydration may be difficult or impossible iii. Acute renal failure		
	For stages I and II, non-bulky (less than 7.5 cm) cases, we recommend the following as first-line treatment: a. Three cycles of R-CHOP followed by ISRT b. Six cycles of R-CHOP with or without ISRT or four cycles of R-CHOP iv. Four cycles of R-CHOP followed by two cycles of rituximab (If IPI is equal to 0)	Strong	Low
What are the treatment strategies for DLBCL among the adult population?	c. For bulky (greater than or equal to 7.5 cm) cases, we recommend six cycles of R-CHOP with or without ISRT. If Rituximab is not available, the next best available therapy is CHOP.	Strong	Low
	For stages III and IV, we recommend R-CHOP or offer to enroll the patient in a clinical trial. If Rituximab is not available, the next best available therapy is CHOP.	Strong	High
	For patients with poor left ventricular function, if available we recommend either the following regimen: a. DA-EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) + Rituximab b. RCDOP (Rituximab, Cyclophosphamide, Liposomal doxorubicin, Vincristine, Prednisone) c. RCEPP (Rituximab, Cyclophosphamide, Etoposide, Prednisone, Procarbazine) d. RCEOP (Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone) e. RGCVP (Rituximab, Gemcitabine, Cyclophosphamide, Vincristine, Prednisolone)	Strong	Low

	For patients with poor left ventricular function, if available we recommend either the following regimen: f. DA-EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) + Rituximab g. RCDOP (Rituximab, Cyclophosphamide, Liposomal doxorubicin, Vincristine, Prednisone) h. RCEPP (Rituximab, Cyclophosphamide, Etoposide, Prednisone, Procarbazine) i. RCEOP (Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone) j. RGCVP (Rituximab, Gemcitabine, Cyclophosphamide, Vincristine, Prednisolone)	Strong	Low
Post-treatment evaluation			
How do we assess or evaluate response to treatment?	Based on clinical evaluation, we recommend offering interim imaging through CT scan with contrast of quality diagnostics after the third cycle of treatment to evaluate early response, then after treatment completion to assess treatment success.	Strong	Low
	For stage I or II patients with complete response, we recommend following up every three to six months for five years, then yearly or as clinically indicated.	Strong	Low
	For stage III or IV patients with complete response, we recommend following up every three to six months for five years, then yearly or as clinically indicated; and imaging on C/A/P/ CT scan with contrast no more often than every six months for two years after completion of treatment, then only as clinically indicated.	Strong	Low

Background

Introduction

DLBCL is characterized by the widespread proliferation of neoplastic B-blasts (Beham-Schmid, 2017). It is the most common type of non-Hodgkin Lymphoma (NHL) (Beham-Schmid, 2017). DLBCL can develop spontaneously or as a result of progression or transformation in patients with low-grade lymphomas, such as chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma, or marginal zone lymphoma (Said, 2013). DLBCL may also represent a last common pathway in a considerable proportion of individuals who have been long-term survivors of indolent lymphoma (Said, 2013).

The usual initial sign of DLBCL is a sudden, painless swelling in the neck, underarms, or groin caused by swollen lymph nodes (Lymphoma Research Foundation, 2020). Swelling may be painful for some individuals. Night sweats, fever, and unexplained weight loss may occur. Patients may also experience fatigue, loss of appetite, dizziness, or discomfort (Lymphoma Research Foundation, 2020). It is considered an aggressive type of disease with constitutional symptoms, necessitating immediate treatment (Liu & Barta, 2019).

DLBCL represents approximately 40% of all cases globally (World Cancer Report, 2014), with a survival rate of 63.9%. That is, about 7 out of 10 patients are more likely to survive after being diagnosed (National Cancer Institute, 2020).

Patients with DLBCL face a significant clinical and economic burden, particularly those who do not react to first-line therapy. Meanwhile, those that are not eligible for transplants have a higher usage of health care resources and expenses, especially in the first 12 months after treatment begins (Yang et al., 2021).

The mortality rate of NHL is up to 259,793 of all deaths worldwide, making it the 11th leading cause of cancer death globally (WHO, 2020). In the Philippines, it ranks 12th in all cancer-caused mortalities, with 2,415 deaths (WHO, 2020).

DLBCL affects both men and women, though it is slightly more prevalent in the male population (Beham-Schmid, 2017; National Cancer Institute, 2020). It can develop in childhood, but its incidence normally increases with age, with approximately half of individuals over the age of 60 being diagnosed with the disease (Lymphoma Research Foundation, 2020).

DLBCL treatments incur prohibitive costs. This is mainly attributed to the recommended treatment regimen and imaging to evaluate the patient's response to treatment. Despite this, there is no PhilHealth benefit package covering the diagnostics, management, and surveillance of DLBCL.

Guideline Development Process

Phase 1 – Preparation Phase

Establishment of the Guideline Development Group

The guideline development group was composed of policy makers, program managers, hematologists and transfusion medicine specialists, medical oncologists, radiation oncologists, pathologists, radiologists and patient group. The multidisciplinary and multispecialty professionals composed the relevant working groups of the DLBCL NCPG, the Technical Advisory Group (TAG), the Steering Committee (SC), the Evidence Review Experts (ERE), and the Consensus Panel (CP).

The TAG and the SC comprised the lead NCPG developers. The TAG has the oversight function to ensure a quality and inclusive NCPG development process. Nominated members for the TAG included representatives from East Avenue Medical Center, the Department of Health, and the Philippine Health Insurance Corporation.

The multidisciplinary SC drafted the scope and target audience of the NCPG. They also identified, ranked, and finalized the clinical questions on diagnosis and clinical management of DLBCL in the Philippines. The SC identified, invited, reviewed, and managed the COI of the relevant working groups, such as the steering committee, evidence reviewers, consensus panelists, and facilitators.

The ERE provided technical assistance in evidence review ranging from the development of the clinical questions, search and identification of evidence, appraisal of relevant literature to answer clinical questions, and synthesis of evidence summaries as the basis of recommendation statements. The ERE for this Guideline included consultants with backgrounds in clinical epidemiology, information specialists, medical informatics, and public health.

The CP was a wider group of DLBCL stakeholders. Establishing a more open and diverse group of stakeholders for the CP — including multidisciplinary healthcare practitioners, patient advocates, DOH program managers, and other technical content experts — was aimed at promoting transparency, introducing different perspectives to DLBCL management, and safeguarding against conflicts of interest. The CP reviewed and revised the recommendation statements and voted on adopting these statements into the Guideline.

Declaration and Management of Conflicts of Interest

The DLBCL NCPG Guideline Development Group utilized the PhP 1,000,000 DOH sub-allotment to develop the guideline. The stakeholders of the working groups that composed the Guideline Development Group (GDG) have declared no competing interests related to this material. The stakeholders included in the guideline development groups were requested to provide a summary of their conflicts of interest (COI) related to DLBCL. These COIs may be classified into financial and non-financial (or intellectual) COI. COIs were reviewed by the ERE, and admission of a stakeholder to the GDG was contingent on the stakeholder having no or minimal COI, following recommendations in the DOH CPG Manual (DOH [Philippines] 2018). Conflicts of interest(s) and how COIs were managed are presented in Annex A.

Identification of the Scope of the NCPG

The PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes and Health Care Setting (ADAPTE Collaboration, 2009). These five items aided the selection and framing of clinical questions on Population; Intervention of interest – screening, diagnostics, and treatment/management; Professionals to whom the guideline will be targeted; specific Outcomes; and Health care setting and context that the guideline will be implemented.

Generation of NCPG Questions

The methodology of clinical question generation is based on frameworks of clinical practice guidelines (CPG), agenda-setting, and consensus-building (Murphy et al, 1998; The James Lind Alliance, 2020; WHO, 2014). For CPG question development guidelines, we specifically referred to guidance published by the WHO in 2014. Due to the COVID-19 pandemic and mobility restrictions at the time of guideline development, all methods of communication were virtual; no face-to-face, physical gatherings were conducted.

PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes, and Health Care Setting (ADAPTE Collaboration, 2009).

Table 2. PIPOH Framework for the DLBCL NCPG Development

Population	Adult (19 years old and above), including elderly, newly diagnosed, not relapse patients
Intervention	Diagnostics and management
Professionals	Medical specialist and allied health professionals

Outcomes	Overall survival rate, disease-free survival, recurrence, and remission
Healthcare Setting	Tertiary level of care (hospital or medical centers)

These guidelines included relevant questions on diagnosis and clinical management of DLBCL. The objectives are the following:

1. To present and synthesize the best available evidence on the diagnosis and clinical management of Diffuse Large B-Cell Lymphoma;
2. To standardize the diagnosis and clinical management of Diffuse Large B-Cell Lymphoma in the Philippines for the reduction of the burden of disease; and,
3. To complement the existing DOH program mandates on cancer control by providing evidence to its statements for policy implementation.

The generation of CPG questions is an essential early step in CPG development. These questions were used as the basis for the subsequent systematic review of the evidence base on DLBCL (WHO, 2014). CPG questions generated by the SC were agreed to focus on evidence uncertainties, areas of controversy in the management of DLBCL and known variations of clinical practice and care especially in the resources available in the Philippine setting. The SC was then convened in virtual workshops where the final questions were formulated in PICO (Population, Intervention, Comparator, and Outcome) format, reviewed, and prioritized according to a consensus. Technical working groups were assigned for further review and revision to reach the final PICO format of the clinical questions. The final list of PICO elements for each CPG question is located in Annex C.

Phase 2 – Evidence Synthesis

Overview of Evidence Synthesis Methods

Considering the time and resources to produce quality CPGs, it is recommended that existing guidelines be adapted to reduce duplication of effort and update existing guidelines in a shorter period of time. In this CPG development process, guideline adaptation by the ADAPTE method was considered to address specific health questions generated. Independent methodologists and reviewers determined if adaptation of any existing CPG was feasible and consequently created the evidence base and recommendation matrix.

The ERE utilized the ADAPTE method to review existing guidelines for inclusion in the evidence base and drafting of recommendation matrix. The ADAPTE collaboration has developed a systematic approach to aid in the adaptation of guidelines (ADAPTE Collaboration, 2009). The systematic approach aids in the use and modification of

existing guidelines to customize an existing guideline to suit the local context while addressing relevant health questions. A systematic search of existing guidelines in multiple databases, including PubMed, Google Scholar and Scopus®. Search terms and limits are provided in Annex B. Updated versions of the guidelines were also searched to ensure currency of the recommendations. Assessment of the guidelines yielded from the systemic search were then given consideration for adaptation by assessment if it meets the qualities of a high-quality guideline using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument as well as if it can address the specific clinical questions. The AGREE II instrument provides a framework for assessing the quality of CPGs (Brouwers et al, 2013). The 23 items in the AGREE instrument assess the methods used for developing the guideline and quality of reporting. Assessment is focused on the rigor and overall score. The domains and criteria for the AGREE II tool are shown in Annex B. The guidelines were assessed for guideline quality, currency, content, consistency, and applicability (ADAPTE Collaboration, 2009). The characteristics and contents of the source guidelines are summarized in Annex B.

Phase 3 – Evidence to Recommendation

The ERE drafted the initial recommendation statements to include level of evidence based on the source guidelines and its references. All guidelines included utilized by recommended Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for evaluation of level of evidence (Schünemann et al, 2013). This is the tool developed by the GRADE working group in evaluating the quality of the evidence and is summarized and defined in Table 3 below.

Table 3. Quality of Evidence Grades (Schünemann et al, 2013)

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The recommendation matrix developed was for finalization of the CP who were provided by the ERE with a guide on determining the strengths of recommendation (Schünemann et al, 2013). Recommendations may either be strong or weak. Strong recommendations refer to issues where the guideline development group may be

confident that the benefits outweigh the risks or costs of an intervention, or vice versa, whereas weak recommendations are those where there is appreciable uncertainty on the calculus of benefits and risks. A summary of the implication of recommendation strength on each type of guideline user based on WHO which is reproduced in full in Table 4.

Table 4. Implications of Strong and Weak Recommendations for Different Users of Guidelines (WHO, 2014)

Guideline Users	Strong Recommendation	Weak Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Phase 3 – Consensus Development

The consensus panel facilitator led the asynchronous consensus-building process through the eDelphi process. The facilitator sent out the three batches of recommendations from the ADAPTE evidence evaluation and synthesis for scrutiny

by the consensus panelists. There are three iterations for comments discussions followed by a presentation of the evidence and nominal group technique discussions (NGT) of recommendations (Delbecq et al., 1986).

Following the NGT discussions, the CP was allowed to revise the recommendation statements for adaptation and contextualization within reasonable limits as long as the revision did not alter the value of the underlying evidence. The facilitator was allowed only to clarify the comments by asking probing exploratory questions. There were no leading questions asked.

The CP set the 80% consensus agreement on every content and strength of each recommendation. The CP repeated the cycle of discussions for content and strength and recommendations that could not reach the consensus marker.

The invited patient and advocacy group attended the consensus panel meeting and encouraged to share practical and lived experiences to improve patient care management and safety.

Patient Values, Preferences, and Other Considerations

There is an advocacy group and no patient nor patient groups present within the SC or CP, results based on a systematic review of patient or family values, was assessed vis-à-vis the recommendations of the GDG after consensus made.

The SC and CP thoroughly discussed the applicability of the recommendations using several criteria, such as improvement of treatment outcomes, acceptability to local professional practice, public health impact, and healthcare cost based on lived experiences.

Ethics review was sought and approved by the DOH Single Joint Review Board.

External evaluation was sought by the guideline development group through expert feedbacks were documented, discussed with the SC and CP then incorporated in the final manuscript.

The DOH as funding agency and EAMC as fund manager did not influence the editorial independence of the GDG.

Dissemination and Use of the Guideline

The value of a CPG is fully appreciated when it is widely adopted, and adoption is contingent on access and distribution of the CPG to its target audience. This clinical practice guideline is available on the DOH website.

The GDG will work closely with DOH and other partners to ensure wide dissemination of the guideline through different events: (1) Presentation in professional society's scientific fora; (2) Distribution of the guideline will be done electronically through DOH and partner society websites; (3) Monitoring/assessment on the uptake of the guideline will be done through monitoring the number of downloads and request for distribution, and; (4) Health outcomes will be monitored during the first three years of guideline distribution specifically on number of cases identified, treated and surveillance for recurrence reported.

The NCPG recommendations are valid until new significant evidence emerges that would require a change in recommendation. The ERE recommends revisiting the Guidelines regularly every three years. The research recommendations may be considered by policymakers and program managers for future research funding as part of the continuous quality improvement of healthcare services in the country.

References

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Clinical Practice Guidelines

Diffuse Large B-Cell Lymphoma National Clinical Practice Guidelines Recommendations

Diagnosis

Question 1. What are the mandatory tests to diagnose and subclassify DLBCL (de novo and transformed cases)?

Recommendations 1a.

We recommend excisional biopsy, immunohistochemistry (staining for pan-B cell markers such as *CD19, CD20, CD22 and CD79a*) and conventional karyotyping to diagnose for DLBCL suspected patients.

Strong recommendation, Low quality of evidence

Recommendations 1b.

When the lymph node is not easily accessible for excisional (or incisional) biopsy, we suggest a combination of core biopsy and FNA biopsies in conjunction with appropriate and available ancillary techniques for the differential diagnosis.

Weak recommendation, Low quality of evidence

Consensus Issues

The Consensus Panel (CP) adopted the National Comprehensive Cancer Network (NCCN) recommendation with modifications in the diagnostic procedures to be conducted, which should depend on non-inferiority, accessibility and affordability. The CP suggested that an adequate sample with optimal fixation can be done, with an H&E morphology plus immunohistochemistry on the mandatory tests, to diagnose and subclassify de novo and transformed cases of DLBCL.

The CP discussed in detail that staining for Pan B cell markers has known limitation to subclassify DLBCL (de novo and transformed cases). In addition, the ERE noted that there are some reservations to recommend the routine use of conventional karyotyping to diagnose suspected DLBCL patients.

In situations where immunohistochemistry is not available (hence, DLBCL diagnosis cannot be done), it is recommended to refer patients to tertiary care centers of excellence for treatment can be initiated by the medical oncologists or hematologists or after going through a multidisciplinary team discussion.

Summary of Evidence

The use of fine-needle aspiration (FNA) biopsy is insufficient to diagnose lymphoma (Henh et al., 2006; Meda et al., 2000). However, when combined with immunohistochemistry (IHC) and flow cytometry, the FNA's diagnostic accuracy improves dramatically (Dong et al., 2001; Jeffers et al., 1988; Zeppa et al., 2004).

According to NCCN, although a core needle biopsy is not ideal for diagnosing B-Cell lymphomas, it may be used in specific situations where it is the only safe way to obtain diagnostic tissue. For differential diagnosis, core needle and FNA biopsies can be employed in conjunction with appropriate ancillary procedures.

When the result is non-diagnostic, a re-biopsy should be done. According to Meda et al. (2000), lymphoma was found in 158 of 290 total aspirates. They mentioned that, on the basis of combined FNA and FC, a conclusive diagnosis of non-Hodgkin's lymphoma (NHL) was achieved in 76.7% (158/206) of lymphoma cases, including 72.3% (86/119) of original lymphomas and 83% (72/87) of previously diagnosed or recurrent lymphomas. Diagnostic sensitivity and specificity were 95% and 85%, respectively, when diagnoses suggestive of lymphoma were deemed positive for lymphoma. FNA and flow cytometry immunophenotyping are clearly complimentary and eliminate the need for a more invasive open biopsy in many lymphadenopathy patients.

Research Recommendation

The GDG recommended the conduct of a costing study on immunohistochemical analysis to diagnose DLBLC.

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Question 2. What tests are needed to determine the extent of DLBCL?

Recommendation 2a.

We suggest the following diagnostic work-up to determine the extent of the disease among newly diagnosed DLBCL patients:

a. Clinical evaluation (history, physical and neurologic examination);
b. Chest/abdomen/pelvic CT scan with contrast of quality diagnostics;
c. For patients with neurologic findings on clinical evaluations, lumbar puncture with evaluation of cerebrospinal fluid;
d. For patients with high-risk CNS manifestation [including those with greater 1 extra nodal site or certain extra nodal sites (kidney, adrenal gland, testis)] or with neurologic manifestations (re mass effect), offer head or neck CT scan or MRI with contrast of quality diagnostics; and,
e. If CT scan is inconclusive or PET/CT scan is equivocal, offer bone marrow biopsy.

Weak recommendation, Low quality of evidence

Consensus Issues

The CP adopted the recommendation with modifications that the proposed tests should be done on a case-to-case basis. This is due to concerns on accessibility and affordability. Although the Panel members recognized the benefits of Positron Emission Tomography/Computerized Tomography (PET/CT) scans, there is currently a lack of available facilities in certain parts of the country. As such, the CP decided not to recommend them at this time.

The Panel adopted the suggestion of NCCN regarding omitting bone marrow biopsy based on PET/CT for bone marrow involvement.

The CP adapted the recommendation and suggested that a good neurological exam or CNS analysis be as clinically indicated. The members also indicated that if there are no neurologic manifestations (usually mass effect), then CT/MRI of the brain is not warranted. This should also be followed with regards to the neck area if the PE is normal. It is also not necessary if whole body PET/CT is done.

Summary of Evidence

Based on the NCCN guidelines, testing for serum beta-2-microglobulin levels would be useful in selected DLBCL patients. PET/CT scans are essential for the initial staging where upstaging resulting in altered therapy happens approximately 9% of the time (Juweid et al., 2011). Several studies have proven that fludeoxyglucose (FDG)

PET is fairly sensitive for detection of nodal and extranodal lymphoma prior to treatment (Bangerter et al., 1998; Buchmann et al., 2001; Hutchings et al. 2006; Jerusalem et al., 2001; Menzel et al., 2002; Moog et al., 1997, 1998; Naumann et al., 2004; Partridge et al., 2000; Schaefer et al., 2004; Weihrauch et al., 2002).

However, in general, a staging FDG-PET/CT done using PET/CT scanners and intravenous (IV) contrast provides at least equal, yet likely superior, information compared to FDG-PET and a separately obtained i.v. contrast-enhanced CT (CECT) from a CT scanner (Juweid et al., 2006, 2007; Seam et al., 2007).

PET/CT scan has been considered useful in the initial staging and restaging of patients with lymphoma, with relatively high diagnostic performance in detecting metastasis and bone marrow involvement. A systematic review of 14 studies (n = 854) showed that FDG-PET/CT scan has a pooled sensitivity of 90.9% (95%CI, 88% to 93.4%) and a pooled specificity of 89.7% (86.2 to 92.6) in detecting metastasis. Based on studies involving 654 newly diagnosed DLBCL patients, FDG-PET/CT scan was also found to be accurate to detect bone marrow involvement. The pooled sensitivity was 88.7% (95% CI, 82.5 to 93.3) and pooled specificity was 99.8% (95% CI, 98.8 to 100%).

Research Recommendation

The GDG recommended the conduct of a costing study on the PET/CT scan as a routine diagnostic work-up for newly diagnosed DLBCL patients.

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PET/CT Scan and Bone Marrow Biopsy

Isasi, C. R., Lu, P., & Blaufox, M. D. (2005). A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *104*(5), 1066-1074.

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CT/MRI

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Treatment and Care

Question 3. What essential tests are needed prior to starting treatment and how frequent are these tests monitored during treatment?

Recommendation 3a.

We recommend the following pretreatment evaluation among newly diagnosed DLBCL patients:

a. Clinical evaluation (*routine*)
   i. History to identify evidence of comorbidities (heart and renal dysfunction)
   ii. Physical examination on lymph node-bearing areas (Waldeyer's ring) and size of liver and spleen
   iii. Neurologic assessment

b. Laboratory studies (*routine*)
   i. Complete blood count with differential count
   ii. Serum chemistries [electrolytes (i.e., calcium, phosphorous), kidney and liver function tests, uric acid, and lactate dehydrogenase]
   iii. Hepatitis screening
   iv. HIV test among high-risk population

c. Imaging (*routine and based on clinical evaluation*)
   i. Left ventricular ejection fraction assessment through echocardiogram

Strong recommendation, Low quality of evidence

Consensus Issues

The CP members adopted the NCCN recommendation in the care and treatment of DLBCL. The members also suggested that specific diagnostic procedure adjustments should be done on a case-by-case basis, depending on the technique's accessibility and affordability.

Summary of Evidence

According to NCCN, the essential work-up procedures include a comprehensive physical examination, with special attention to node-bearing areas and the size of the liver and spleen, as well as laboratory tests including a complete blood count (CBC), serum lactate dehydrogenase (LDH), hepatitis B virus (HBV) testing, comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless coexistent renal insufficiency). When anthracyclines and anthracenedione-

containing regimens are administered, multigated acquisition (MUGA) scans or echocardiograms are indicated.

In the phase 3 study (n=2797) of Kusumoto et al. (2019), HBV DNA monitoring–guided preemptive nucleos(t)ide treatment can prevent HBV hepatitis during anti-CD20 immunochemotherapy in B-Cell NHL. HBV carriers with lymphoid malignancies are at an increased risk of HBV reactivation and illness, particularly those on anti-CD20 MAB-based regimens (Yeo et al., 2004). A robust link between hepatitis C virus (HCV) seropositivity and the development of B-Cell lymphomas have also been documented (Arcaini et al., 2007; Engels et al., 2004; Nieters et al., 2006).

On the other hand, in the NICE guidelines, patients in complete remission after first-line treatment with curative intent for DLBCL should be offered regular clinical assessments. This included a regular clinical assessment aimed at detecting relapse after completing treatment for people in ongoing complete remission. It was also noted that early diagnosis of relapse and timely re-treatment to improve survival prospects are the goals of follow-up throughout the first two to three years.

Follow-up visits often include a review of symptoms, a physical examination, CBC, and a biochemical profile, including serum LDH. Although the follow-up strategy has yet to be determined, considering the majority of relapse cases occur during the first two years, most patients are seen every two to three months.

NICE recommended LDH surveillance for detecting relapse. According to Hiniker et al., (2015), in their retrospective study on 162 stage I and II DLBCL patients, no relapses were found using surveillance by LDH (freedom from progression 0.08; HR, 95% CI 1.9, 0.9-3.8).

Routine surveillance imaging, such as chest X-ray, CT, and PET-CT, is also not recommended for detecting relapse in people who are asymptomatic (NICE, 2021).

In the clinical study evaluating the role of routine imaging versus symptom-directed unplanned visits, a total of 856 outpatient department (OPD) visits were recorded. Out of 856, there were 501 visits with routine imaging, 322 visits without routine imaging, and 33 unscheduled early visits due to abnormal symptoms (3.9%) (Hong et al., 2014). Recurrence was observed in 15 of the 106 patients studied (median follow-up duration of 38.1 months). Compared with enhanced CT scan, FDG-PET/CT showed a higher rate of false-positive results (7/407 [1.7%] for CT vs. 23/165 [13.7%] for FDG-PET/CT), suggesting that the results of routine imaging are unsatisfactory, causing patients to have unnecessary biopsies or additional scans due to the false-positive results.

Research Recommendation

The GDG recommended the conduct of a costing study on the inclusion of hepatitis screening on the management of newly diagnosed DLBLC patients.

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Question 4. What is the role of Tumor Lysis Syndrome (TLS) prophylaxis in DLBCL?

Recommendations 4a.

We recommend prophylaxis for tumor lysis syndrome whenever available and/or accessible to patient. The following prophylactic strategies should be considered:

a. Allopurinol
b. Febuxostat, if intolerant to Allopurinol
c. Rasburicase (*if available*), if with the following conditions:
    i. Patient with urgent need to initiate therapy in a high bulk patient
    ii. Situations where adequate hydration may be difficult or impossible
    iii. Acute renal failure

Strong recommendation, Low quality of evidence

Consensus Issues

TLS prophylaxis and strategies

The CP members adopted the NCCN recommendation and specified that TLS should be offered based on clinical indications.

Summary of Evidence

TLS Prophylaxis

Tumor Lysis Syndrome (TLS) is an oncologic emergency due to the acute release of potentially damaging intracellular contents into the systemic circulation. This happens during rapid tumor cell disintegration induced by chemotherapy and/or other interventions like embolization or radiation. Its symptoms include hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and acute kidney injury (AKI), often with progressive oliguria (Shaban, 2022). It is usually observed within 12 to 72 days post-chemotherapy (Coiffier et al., 2008).

TLS is currently classified by laboratory or clinical parameters. Laboratory TLS is clinically silent and is defined by at least two of the following laboratory findings three days before or seven days after initiation of chemotherapy: hyperuricemia (25% increase), hyperkalemia (25% increase), hyperphosphatemia (25% increase), and hypocalcemia (25% decrease). Clinical TLS pertains to laboratory TLS that is complicated by at least one of the following complications: severe renal impairment, cardiac arrhythmias, central nervous system toxicity, and/or death (Cairo & Bishop, 2004). DLBCL is considered as one of the risk factors for developing TLS (Cairo et al., 2010).

TLS prophylaxis is mainly based on intravenous (IV) hydration and the use of hypouricemic agents. The cornerstone of preventing TLS is aggressive IV hydration, which is indicated prior to therapy in all patients at intermediate or elevated risk for TLS. The purpose of IV hydration is to increase renal perfusion and glomerular filtration and to induce high urine output to reduce the likelihood of uric acid or calcium phosphate precipitation in the tubules (Larson & Pui, 2022). Optimal management of TLS is possible if it is anticipated and when the medications are started prior to chemotherapy (Cairo et al., 2010).

Strategies for TLS Prophylaxis

The NCCN (2022) recognizes the higher risk of developing TLS among patients with DLBCL after chemotherapy, apart from Burkitt lymphoma, chemosensitive, rapid proliferative or aggressive hematologic malignancies, elevated leukocyte count, pre-existing elevated uric acid, renal disease, or renal involvement. TLS prophylaxis is achieved by hydration and management of hyperuricemia using Allopurinol, Febuxostat, and Rasburicase (NCCN, 2022).

Allopurinol, which is considered as first-line therapy for adults, is administered at 100 mg/m^2 every eight hours (maximum dose of 800mg per day) (Coiffier et al., 2008). IV Allopurinol can be given at a dose of 200 to 400 mg/m^2 per day for patients who are unable to take oral medications (Feusner & Farber, 2001; Smalley et al., 2000).

A meta-analysis of six studies between 2014 and 2017 (n=659; 331 treated Febuxostat and 328 treated with Allopurinol) evaluating the efficacy and safety of Allopurinol and Febuxostat as TLS prophylactic showed that Febuxostat and Allopurinol have similar response rate (odds ratio [OR]: 1.01, 95% CI: 0.55-3.51) and TLS incidence (OR: 1.01, 95% CI: 0.56-1.81). Additionally, serum uric acid levels did not differ between the Febuxostat and Allopurinol groups on day two (mean difference: -0.21 mg/dL, 95% CI: -1.30 to 0.88) and day seven (mean difference: -0.43 mg/dL, 95% CI: 1.38-0.51) of treatment (Bellos et al., 2019). Febuxostat is given at a dose of 120 mg (oral) daily and is used for patients who cannot tolerate Allopurinol (Shaban, 2022).

In a randomized trial comparing the efficacy and safety of Febuxostat and Allopurinol in 346 adult patients with hematologic malignancies at intermediate or elevated risk for TLS, a fixed dose of Febuxostat provided a significantly superior serum uric acid control compared to Allopurinol while maintaining comparable renal function and safety. The mean serum uric acid (sUA) was significantly lower for Febuxostat than for Allopurinol (514.0 ± 225.71 versus 708.0 ± 234.42 mg × h/dl; P<0.0001) (Spina et al., 2015).

Rasburicase is a recombinant urate oxidase which catalyzes uric acid oxidation to a non-toxic metabolite. In a prospective multicenter phase III trial comparing the efficacy

and safety of Rasburicase and Allopurinol in adult patients with hematologic malignancies at risk for having TLS, Rasburicase was superior to Allopurinol (P=0.001) in the overall study population, in patients at high risk for TLS (89% v 68%; P=0.012), and in those with baseline hyperuricemia (90% v 53%; P=0.015) (Cortes et al., 2010).

In a systematic review of four RCTs and 17 observational studies (n=1261; 768 received Rasburicase), the researchers concluded that while Rasburicase was effective at lowering serum uric acid levels in adults with or at risk of TLS, there was insufficient evidence to determine whether clinical outcomes were improved when compared to other therapeutic alternatives.

In the observational studies, 7.4% of patients had clinical TLS after receiving Rasburicase (95% CI, 1.7%-16.7%), 93.4% of patients achieved normal serum uric acid levels after Rasburicase treatment (95% CI, 91.7%-94.6%), 4.4% ended up having acute kidney injury (95% CI, 3.0%-6.0%), and 2.6% died (95% CI, 0.95%-5.0%) (Lopez-Olivo et al., 2013).

Research Recommendation

The GDG recommended no additional research.

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TLS prophylaxis

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Question 5. What are the treatment strategies for DLBCL among adult population?

Recommendations 5a.

For stages I and II, non-bulky (less than 7.5 cm) cases, we recommend the following as first-line treatment:

a. Three cycles of R-CHOP followed by ISRT
b. Six-cycles of R-CHOP with or without ISRT or four cycles of R-CHOP
c. Four cycles of R-CHOP followed by two cycles of rituximab (If IPI is equal to 0)

Strong recommendation, Low quality of evidence

Recommendations 5b.

For bulky (greater than or equal to 7.5 cm) cases, we recommend six cycles of R-CHOP with or without ISRT. If Rituximab is not available, the next best available therapy is CHOP.

Strong recommendation, Low quality of evidence

Recommendations 5c.

For stages III and IV, we recommend R-CHOP or offer to enroll the patient in a clinical trial. If Rituximab is not available, the next best available therapy is CHOP.

Strong recommendation, High quality of evidence

Recommendations 5d.

For patients with poor left ventricular fraction, if available we recommend either the following regimen:

a. DA-EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) + Rituximab
b. RCDOP (Rituximab, Cyclophosphamide, Liposomal doxorubicin, Vincristine, Prednisone)
b. RCEPP (Rituximab, Cyclophosphamide, Etoposide, Prednisone, Procarbazine)
c. RCEOP (Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone)
d. RGCVP (Rituximab, Gemcitabine, Cyclophosphamide, Vincristine, Prednisolone)

Strong recommendation, Low quality of evidence

Consensus Issues

First-line therapy (Stages I and II, non-bulky)

The CP voted to adapt the recommendation from the DLBCL-NCCN2021. One issue identified by one Panel member is the unavailability of rituximab in some settings. It was suggested that CHOP should be given as an alternative to R-CHOP in such areas.

Another issue identified is the limited availability of PET/CT scan. The suggested resolution to this concern is to use standard CT scan with contrast as an alternative to PET/CT scan.

First-line therapy (Bulky)

The Panel members decided to adopt the recommendation but suggested to indicate that in areas where rituximab is not available, the next best therapy is CHOP. In places where PET/CT scan is not accessible, the second option is CT scan with contrast.

It was also proposed that identification of radiotherapy facilities should be well-situated for every region or nearby provinces, with a designated apex hospital.

First-line therapy (Stages III and IV)

The Panel members voted to adopt the recommendation yet reiterated that in areas where rituximab is not available, the next optimal therapy is CHOP. If PET/CT scan is not accessible, CT scan with contrast should be given to patients.

First-line therapy (Patients with poor left ventricular function)

The CP adapted the recommendation from the DLBCL-NCCN2021, under section BCEL-C. Like the previous sections, one Panel member noted that rituximab is not available in some settings. In such areas, CHOP should be given as an alternative to R-CHOP.

The limited availability of PET/CT scan was again mentioned. The use of standard CT scan with contrast was suggested as an alternative.

Another Panel member agreed with the use of liposomal doxorubicin and/or protocols without the standard doxorubicin (National Comprehensive Cancer Network, 2021).

Summary of Evidence

First-line therapy (Stages I and II, non-bulky)

Six cycles of Rituximab + Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) are deemed to be one of the standard regimens for DLBCL. NCCN recommends it as first-line therapy for Stage I and II, non-bulky DLBCL (<7.5cm).

The MabThera International Trial (MInT) showed that six cycles of R-CHOP is effective for young patients with good-prognosis DLBCL when compared against six rounds of CHOP. R-CHOP had a higher three-year event-free survival (R-CHOP: 79%, 95% CI: 75-83 vs CHOP: 59%, 95% CI: 54–64; log-rank p=0.0001), as well as a higher three-year overall survival (OS) rate (R-CHOP: 93%, 95% CI: 90-95 vs CHOP: 84%, 95% CI: 80-88) (Pfreundschuh et al., 2006).

The FLYER trial assessed whether four cycles of R-CHOP + two doses of rituximab as monotherapy is non-inferior to the standard six cycles of R-CHOP. The three-year progression-free survival (PFS) for the patients given with four cycles of R-CHOP + two doses of rituximab is 96%, which is 3% better than those given six cycles of R-CHOP, showing the non-inferiority of the four-cycle regimen (Poeschel et al., 2019).

The Southwestern Oncology Group (SWOG) S0014 study evaluated the effect of three cycles of R-CHOP plus IFRT in patients with at least one adverse factor (non-bulky stage II, age > 60 years, ECOG PS 2, or elevated serum LDH). The intervention resulted in a PFS of 93% (two years) and 88% (four years), and an OS of 95% (two years) and 92% (four years). These findings were favorable relative to the survival rates of historic group of patients treated without rituximab (four-year PFS: 78% and OS rate: 88%) (Persky et al., 2008). Three cycles of R-CHOP + RT is also associated with significantly lower risk of second-line therapy and lesser incidence of neutropenia including cases requiring hospitalization (Odejide et al., 2015).

A prospective randomized trial in patients with non-bulky limited-stage DLBCL was also done to investigate the benefit of RT after giving four or six cycles of R-CHOP versus four or six cycles of R-CHOP without RT. The five-year event-free survival was not statistically significant between the two groups (R-CHOP + RT = 92% vs R-CHOP = 89%, HR=0.61, 95% CI: 0.3-1.2; P=0.18). OS was also not significantly different (R-CHOP + RT = 96% vs R-CHOP = 92%). The study demonstrated that R-CHOP followed by RT is not inferior to R-CHOP alone (Lamy et al., 2018).

First-line therapy (Bulky)

For patients with Stage I/II disease, findings from the RICOVER-noRTh trial indicated that there was a substantial benefit if radiotherapy was added to initial bulky sites ≥7.5

cm. Moreover, studies such as Held et al. (2014) and Pfreundschuh et al. (2011), showed that R-CHOP (six cycles) with or without involved site radiotherapy (ISRT) is recommended for patients with bulky disease (≥7.5 cm).

First-line therapy (Stages III and IV)

In advanced-stage DLBCL cases, several randomized trials, particularly Coiffer et al. (2002, 2010), Habermann et al. (2006), Sonneveld et al. (2005), have denoted the efficacy of R-CHOP-21 for treatment.

Furthermore, the GELA study (LNH98-5), which evaluated eight cycles of R-CHOP compared to CHOP in older patients (60–80 years old; n=399), presented rates of ten-year PFS (37% vs. 20%), DFS (64% vs. 43%), and OS (44% vs. 28%) that were significantly higher for those who were given R-CHOP. These findings were then confirmed among younger patients with a zero or one risk factor according to the IPI, in the MinT study (six cycles of R-CHOP or CHOP), and also in patients older than 60 years in The Dutch HOVON and Nordic Lymphoma Groups (eight cycles of R-CHOP-14 or CHOP-14) and ECOG/CALGB study.

In the RICOVER 60-trial, the addition of rituximab to six or eight cycles of CHOP-14 (R-CHOP-14) significantly improved clinical outcomes, versus CHOP-14 alone. In this study, older patients (age 61–80 years) were randomized to receive CHOP-14 (six or eight cycles) with or without eight cycles of rituximab, and RT was administered to initial bulky disease sites with or without extranodal involvement. R-CHOP-14 was associated with significantly improved EFS, and OS compared to CHOP-14 ($P<0.001$), for a median follow-up of 78 months. It was therefore concluded that in this patient group, six cycles of R-CHOP-14 combined with eight doses of rituximab should be the preferred regimen.

First-line therapy (Patients with poor left ventricular function)

NCCN recommends the use of either DA-EPOCH + rituximab, RCDOP, RCEPP, RCEOP, or RGCVP as first-line therapy for patients with poor left-ventricular function. While there are limited published studies concerning these medications, NCCN member institutions are already using these for first-line treatment of very frail DLBCL cases, those with poor left ventricular function, and patients older than 80 years of age who also have comorbidities.

A prospective, multi-institutional phase II study was done to assess the efficacy and safety of DA-EPOCH + rituximab in untreated patients with poor prognosis DLBCL (n=81). Complete response was seen in 80.2% of patients. The ten-year event-free survival was 47.8% and the OS was 63.6%. Use of DA-EPOCH + rituximab showed a tolerable toxicity profile and acceptable long-term outcome (Purroy et al., 2015).

NCCN emphasized that doxorubicin should be maintained at base dose if upward dose adjustment of the DA-EPOCH + rituximab regimen is needed.

A study on RCDOP for elderly patients with DLBCL presented an overall response and complete response rate of 76% and 59%, respectively, with a projected two-year EFS of 65.5% and OS of 68.5%. LVEF and troponin levels had no significant changes during the entire treatment period, although one patient with a history of atrial fibrillation was reported to have a single episode of arrhythmia (Zaja et al., 2006).

In another study, RCEOP was evaluated as an alternative to R-CHOP in patients who are contraindicated to using anthracyclines. Five-year time to progression for RCEOP and R-CHOP were not statistically different (57% vs 62%; $P = 0.21$). The five-year OS is lower for the RCEOP versus R-CHOP (49% vs 64%; $P = 0.02$) (Moccia et al., 2009).

A single arm, multicenter phase II trial investigated the possible use of RGCVP in patients with cardiac comorbidity and unfit for anthracycline-containing chemoimmunotherapy. Thirty-eight out of 61 patients who received RGCVP achieved disease response (61.3%, 95% CI: 49.2-73.4). Two-year PFS was 49.8% (95% CI: 37.3-62.3), and two-year OS was 55.8% (95% CI: 43.3-68.4). Thirty-four patients had hematologic toxicity ≥ grade 3, and 15 cardiac events were documented, seven of which were grade 1 to 2, five were grade 3 to 4, with three fatal events, indicating the study population's poor cardiac status (Fields et al., 2014).

In a study among patients treated with RCEPP (n=83), the overall response rate was 72%, which concluded that RCEPP can be considered in some patients who are unable to tolerate doxorubicin-containing regimens (Chao et al., 1990).

Research Recommendation

The GDG recommended no additional research.

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First-line therapy (Stages III and IV)

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Post-treatment Evaluation

Question 6. How do we assess or evaluate response to treatment?

Recommendations 6a.

Based on clinical evaluation, we recommend offering interim imaging through CT scan with contrast of quality diagnostics after the third cycle of treatment to evaluate early response, and after treatment completion to assess treatment success.

Strong *recommendation, Low quality of evidence*

Recommendations 6b.

For stage I or II patients with complete response, we recommend following up every three to six months for five years, then yearly or as clinically indicated.

Strong recommendation, Low quality of evidence

Recommendations 6c.

For stage III or IV patients with complete response, we recommend following up every three to six months for five years, then yearly or as clinically indicated; and imaging on C/A/P/ CT scan with contrast no more often than every six months for two years after completion of treatment, then only as clinically indicated.

Strong recommendation, Low quality of evidence

Consensus Issues

Interim Imaging

The CP voted to adopt this recommendation of interim imaging after three cycles of treatment. However, it was noted that standard CT scan and/or MRI may be the only imaging tools for assessment in certain regions. As such, there should be an option of using CT scan with contrast in areas where PET is not available.

R-CHOP and FDG-PET-CT imaging

The Panel voted to adapt the NCCN and NICE recommendations on restaging DLBCL after three to four cycles of R-CHOP. The Panel also mentioned that it is good practice to re-evaluate response mid-cycle. If the patient has financial constraints, re-evaluation at the end of the treatment can be done. The use of CT scans may be used as surveillance in the locality and in major hospitals in the country.

Interim Restaging – Stage I, II

The CP adapted the recommendation and stated that CT scan can be given when PET is not available. In addition, the standardization or evaluation of the accuracy of modernized CT scan should be done. This will help clinicians in their assessment of lymphoma patients.

Interim Restaging – Stage III, IV

The Panel members chose to adapt the recommendation with minor modifications. They suggested the option of performing CT scan if PET cannot be done and for the provision of modernized CT scan and/or MRI in most healthcare institutions.

Summary of Evidence

Interim Imaging

According to the NCCN guidelines, interim restaging is done to identify patients whose disease has not responded to or has progressed on induction therapy. Various studies have shown that a negative PET scan after two to four cycles of induction therapy is associated with significantly higher EFS and OS rates (Dupuis et al., 2009; Haioun et al., 2005; Mikhaeel et al., 2000).

Interim PET scans, however, can bring out false positive results, and many patients given chemoimmunotherapy have favorable long-term outcomes, even with a positive interim PET scan. In the prospective study done by Moskowitz et al. (2010), the PFS in patients who were interim PET-positive, biopsy-negative (after four cycles of accelerated R-CHOP) was similar to those with a negative interim PET scan. For the retrospective analysis by Pregno et al. (2012), there was only a minor difference in the two-year PFS rates in patients with a positive interim PET scan versus a negative interim PET scan after treatment with six to eight cycles of R-CHOP (72% and 85% respectively; P=0.0475).

In another prospective study, Mamot et al. (2015) evaluated the predictive value of interim PET scans after two cycles of R-CHOP (n=138 patients). The two-year EFS rate was significantly lower for patients with a positive interim PET-scan compared to those with a negative interim PET scan (48% vs. 74%; P=0.004), although the two-year OS was not significantly different between the two groups (88% vs. 91%; P=0.46). On the other hand, the PETAL trial demonstrated that a positive interim PET scan (change in SUVmax of <66%) was associated with significantly inferior EFS and OS. However, PET-based treatment intensification did not improve outcomes in patients given R-CHOP.

It is then not recommended to use interim PET imaging to guide changes in therapy. If treatment modifications are based on interim PET scan results, a repeat biopsy of residual masses must be considered to confirm PET-positivity before additional therapy. The NCCN panel endorsed a waiting time of six to eight weeks after completion of therapy before repeating PET scans. Response assessment by PET/CT should be performed via the five-point scale (5-PS), which is based upon the visual assessment of fluorodeoxyglucose (FDG) uptake in the involved sites relative to that of the mediastinum and liver.

R-CHOP and FDG-PET-CT imaging

According to NCCN, PET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET/CT scan is performed and positive, it is recommended to conduct re-biopsy before changing the course of treatment. Repeat biopsy should be strongly considered if the patient is PET-positive prior to additional therapy. If the biopsy is negative, the PET-negative guideline should be followed.

Isasi et al. (2005) stated in their meta-analysis study that clinicians may choose to employ FDG-PET in the staging procedure since it is useful for staging and restaging lymphoma patients. In the retrospective study of Trotman et al. (2011) on the PET-CT scans performed after induction immunochemotherapy, 32% out of 122 PET-CT scans, were reported as positive by the local investigators. Results indicated that patients who remained PET-positive had a PFS rate of 32.9% (95% CI, 17.2% to 49.5%) at 42 months compared with 70.7% (95% CI, 59.3% to 79.4%) in those who became PET negative. According to NCCN, several benign conditions, including sarcoid, infection, and inflammation, can result in false-positive PET scans, complicating the interpretation. Moreover, lesions less than 1 cm are not reliably visualized with PET scans.

Schaefer et al. (2004) noted that PET/CT and contrast-enhanced CT had 94% and 88% sensitivity, respectively, and 100% and 86% specificity. For assessing organ involvement (n=60 patients), PET/CT and contrast-enhanced CT have a sensitivity of 88% and 50%, respectively, and specificity of 100% and 90%. When compared to full-dose diagnostic CT or PET alone, PET/CT has substantial advantages in both staging and restaging (Schaefer et al., 2004; Rodriguez-Vigil et al., 2006).

FDG-PET-CT imaging (at end of treatment, and before autologous stem cell transplantation)

Based on the NICE guidelines, there is clear and strong evidence of benefit for the use of FDG-PET-CT imaging to evaluate response at end of treatment for DLBCL patients.

In Juweid's (2011) study, PET/CT scans were found to be vital for response assessment after treatment, as they can distinguish residual fibrotic masses from masses containing viable tumor. Nonetheless, it should be considered that FDG-PET application for post-therapy surveillance remains disputed, mainly because of false-positive findings, potentially resulting in increasing cost without proven benefit from earlier PET detection of disease compared to standard surveillance methods (Jerusalem et al., 2003).

Furthermore, in high-grade NHL patients, achieving full remission following first-line systemic therapy is critical as it usually leads to a prolonged PFS, whereas an inadequate response is linked to worse patient outcomes. According to NICE, the benefit of FDG-PET-CT imaging to assess treatment response before autologous stem cell transplantation is less certain.

In their retrospective study, Mato et al. (2012) found that PFS (hazard ratio [HR], 0.9; 95% confidence interval [CI]: 0.3-2.7; P=0.8) and OS (HR, 0.6; 95% CI: 0.1-2.9; P=0.5) were not linked with interim PET-CT status. PFS was statistically significantly associated with post-treatment PET-CT status (HR, 5.2; 95% CI: 2.0-13.6; P=0.001), and OS was trending toward significance (HR, 2.8; 95% CI: 0.8-9.6; P=0.07).

Interim Restaging – Stage I, II

As indicated in the NCCN guidelines, for patients treated with ISRT, restaging should be done after completion of first-line chemoimmunotherapy before ISRT is given, since RT dosage will be influenced by the test result. Currently, there are no studies implying that a change in treatment is needed if there is PR with persistent PET positivity after three cycles. If the PET scan is positive after six cycles of R-CHOP or R-CHOP-14, it is appropriate to proceed to high-dose therapy and autologous stem cell rescue (HDT/ASCR) with or without RT.

For patients with CR, it is recommended to do follow-ups at regular intervals (every three to six months for five years, then yearly or as clinically indicated thereafter) when end of treatment restaging is concluded. Follow-up CT scans are proposed only if clinically indicated. On the other hand, patients with PR and with no response to treatment or progressive disease, are managed for relapsed or refractory disease.

Interim Restaging – Stage III, IV

Based on NCCN, the planned course of R-CHOP to a total of six cycles is provided if interim staging (after two to four cycles) yields a CR or PR finding. Upon completion of treatment, the end of treatment restaging will then be performed.

In the RICOVER-noRTh trial (an amendment to the RICOVER-60 trial), 164 patients with stage III-IV disease were given six cycles of R-CHOP-14 and RT to bulky sites or

extranodal involvement was omitted. The three-year PFS and OS rates were significantly inferior, in comparison to the survival rates of patients from the RICOVER-60 trial treated with the same chemoimmunotherapy with RT to bulky sites.

In the MInT and RICOVER-60 trial, it was demonstrated in subgroup analyses that in patients with sites of skeletal involvement, there was significant benefit from RT to said sites. After the end of treatment restaging, observation is preferred for patients with CR. ISRT to initially bulky disease or isolated skeletal sites can be considered.

For CR patients, follow up should be conducted at regular intervals (every three to six months for five years, then yearly or as clinically indicated thereafter). In addition, follow-up imaging CT scans should be conducted no more than every six months for two years after completion of therapy, then only as clinically indicated thereafter. While patients with PR (after completion of initial therapy) and those with no response to treatment or progressive disease are treated for relapsed or refractory disease.

Research Recommendation

The GDG recommended no additional research.

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Interim Imaging

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FDG-PET-CT imaging (at end of treatment, and before autologous stem cell transplantation)

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Interim Restaging – Stage I, II

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ANNEXES

Annex A: GDG COI Declaration and Management

Annex A.1. Technical Advisory Group COI Declaration and Management

Name	Affiliation	Conflict of Interest		
		Intellectual	Financial	Management
Nilo C. de los Santos	East Avenue Medical Center	None	None	May participate in the NCPG development
Clarito U. Cairo, Jr.	Department of Health	None	None	May participate in the NCPG development
Alma B. Abainza-Sanchez	PhilHealth	None	None	May participate in the NCPG development
Samuel S. Duran	East Avenue Medical Center	None	None	May participate in the NCPG development
Allan Troy D. Baquir	East Avenue Medical Center	None	None	May participate in the NCPG development

Annex A.2. Steering Committee COI Declaration and Management

Name	Qualifications	Conflict of Interest		
		Intellectual	Financial	Management
Dr. Ma. Rosario Irene Castillo	East Avenue Medical Center	None	None	May participate in the NCPG development
Dr. Daphne Ang	Philippine Society of Pathologists	None	None	May participate in the NCPG development
Dr. Alejandro Arevalo	Philippine Society of Pathologists	None	None	May participate in the NCPG development
Dr. Cursill Ibay	Philippine College of Radiology	None	None	May participate in the NCPG development
Dr. Irene Bandong	Philippine College of Radiology	None	None	May participate in the NCPG development
Dr. Jay Datukan	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. James Malala	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Priscilla Caguioa	Philippine Society of Medical Oncology	None	None	May participate in the NCPG development
Dr. Ellaine Ilagan-Cargullo	Philippine Society of Medical Oncology	None	None	May participate in the NCPG development
Dr. Kenneth Sy	Philippine Radiation Oncology Society	None	None	May participate in the NCPG development
Dr. Angela Guerlan-Tagle	Philippine Radiation Oncology Society	None	None	May participate in the NCPG development

Annex A.3. Consensus Panel COI Declaration and Management

Name	Qualifications	Conflict of Interest		
		Intellectual	Financial	Management
Dr. Maria Claudia Chavez	East Avenue Medical Center	None	None	May participate in the NCPG development
Ms. Alyanna Riel Panlilio	Department of Health	None	None	May participate in the NCPG development
Dr. Catherine Rosales	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Flordeluna Mesina	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Jomell Julian	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Judy Lee	Philippine College of Hematology and Transfusion Medicine	None	None	May participate in the NCPG development
Dr. Stephen Garcia	Philippine Society of Medical Oncology	None	None	May participate in the NCPG development
Dr. Jasmin Igama	Philippine Society of Medical Oncology	None	None	May participate in the NCPG development
Dr. Christian Cuaresma	Philippine Society of Medical Oncology	None	None	May participate in the NCPG development
Dr. Teresa Sy Ortin	Philippine Radiation Oncology Society	None	None	May participate in the NCPG development

Dr. Dennis Doromal	Philippine Radiation Oncology Society	None	None	May participate in the NCPG development
Dr. Rose Lou Marie Agbay	Philippine Society of Pathologists	None	None	May participate in the NCPG development
Dr. Januario Veloso	Philippine Society of Pathologists	None	None	May participate in the NCPG development
Dr. Jonas Santiago	Philippine College of Radiology	None	None	May participate in the NCPG development
Dr. Khristine Pulido-Brillo	Philippine College of Radiology	None	None	May participate in the NCPG development

Annex B: Summary of ADAPTE Evidence

During the development of the Diffuse Large B-Cell Lymphoma National Clinical Practice Guideline (DLBCL NCPG), ADAPTE methodology was used to take advantage of the existing high-quality guidelines that can be modified or customized to suit the local context while addressing relevant health questions This is a systematic approach that was designed to aid in the adaptation of guidelines by the ADAPTE collaboration using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. This, in turn, provides a framework for assessing the quality of clinical practice guidelines ensuring that high quality guidelines are used for adaptation.

Annex B.1. NCPG PIPOH Framework

Population	Adult (19 years old and above), including elderly, newly diagnosed, not relapse patients
Intervention	Diagnostics and Clinical Management
Professionals	Medical Specialist and Allied Health Professionals
Outcomes	Overall survival rate, disease-free survival, recurrence, and remission
Healthcare Setting	Tertiary Level of Care (Hospital or Medical Centers)

Annex B.2. Search Strategy

The eight previously identified databases were systematically searched for guidelines on DLBCL. The following were the inclusion criteria used for selection of applicable guidelines:

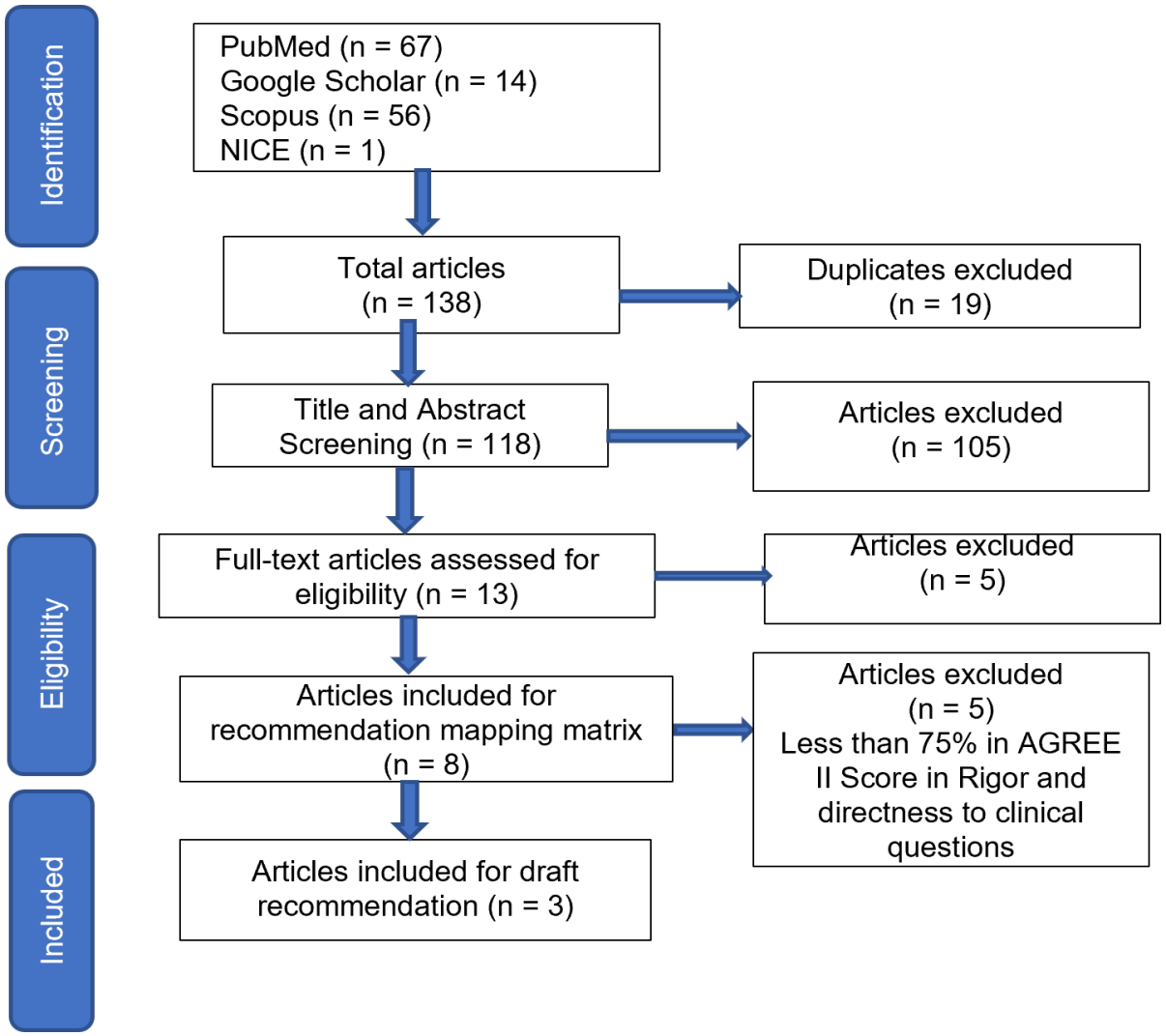
Database	Search String Used
PubMed	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”
Scopus	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”
Google Scholar	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”

Guidelines International Network (GIN)	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”
The National Institute for Health and Care Excellence (NICE)	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”
Scottish Intercollegiate Guidelines Network (SIGN)	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”
EMBASE	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”
Cochrane	Guideline [Publication Type] OR practice guideline [Publication Type] or recommendation*[Title] OR standard* [Title] OR standard* [Title] OR guideline* [Title]) AND "Diffuse Large B Cell Lymphoma”

Search Criteria in Scoping Review

Inclusion Criteria	Exclusion Criteria
1. Clinical practice guidelines for Diffuse Large B-Cell Lymphoma published in the last 10 years (2011 – present)	1. Articles with no available full-text access 2. Articles not written in English and without English translation

Annex B.3. PRISMA Flow



Annex B.4. Guideline Characteristics

Guideline	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence	OVERALL
DLBCL-NCCN2019	86.1	75	63.5	88.9	54.2	83.3	75
DLBCL-NCCN2021	83.3	72.2	61.5	86.1	41.7	79.2	66.7
DLBCL-NICE2021	88.9	80.6	74.0	100.0	70.8	70.8	75

Annex B.5. Guideline Assessment and Selection

The tables below summarize the characteristics of the included guidelines that were evaluated for adaptation. The rigor dimension of the AGREE II instrument was completed by two appraisers who were members of the ERE team for the seven guidelines.

Title	Publisher	Country/ Language	Publication Date	Search Duration	Recommendation Standards	AGREE II Score (Rigor)
NCCN Guidelines Insights: B-Cell Lymphomas, Version 3.2019	National Comprehensive Cancer Network	Plymouth Meeting, Pennsylvania/ English	June 2019	07/21 to 05/22	NCCN Categories of Evidence and Consensus	63.5
B-Cell Lymphomas Version 4. 2021- May 5, 2021	National Comprehensive Cancer Network	Plymouth Meeting, Pennsylvania/ English	May 5, 2021	07/21 to 05/22	NCCN Categories of Evidence and Consensus	61.5
Treating Diffuse Large B-Cell Lymphoma	National Institute for Health and Care Excellence	London, United Kingdom/ English	2021	07/21 to 05/22	N/A	74.0

Annex C. CPG Questions in PICO Framework

Annex C.1. Diagnosis

1. What are the mandatory tests to diagnose and subclassify DLBCL (de novo and transformed cases)?

Population	Intervention	Comparator	Outcomes
Adults with nodal or extranodal mass, suspected of high-grade B-Cell non-Hodgkin's lymphoma (primary and transformed cases)	1. Versus incisional biopsy 2. Versus core needle biopsy	Preferably excisional biopsy of representative neoplastic lymph node and/or extranodal mass; For potentially inaccessible sites, i.e., retroperitoneal or intra-abdominal regions - a minimum requirement of an incisional and/or core needle biopsy with several biopsy tissues/strips for H and E and IHC testing); Preferred fixation: 10% buffered formalin	Diagnostic accuracy, all-cause mortality, DLBCL related mortality, morbidity, false positive, false negative, adverse events, QOL

2. What tests are needed to determine the extent of DLBCL?

Population	Intervention	Comparator	Outcomes
Adults with confirmed DLBCL 5. Patients with high risk of CNS involvement	1. Serologic exam 2. Chest x-ray 3. Ultrasound 4. CT Scan (neck, chest, abdomen) 5. MRI (with contrast) 6. PET - CT (with contrast)	Bone marrow biopsy	Diagnostic accuracy, all-cause mortality, DLBCL related mortality, morbidity, false positive, false negative, adverse events, QOL

Annex C.2. Treatment and Care

3. What essential tests are needed prior to starting treatment and how frequent are these tests monitored during treatment?

Population	Intervention	Comparator	Outcomes
Adults with confirmed DLBCL	1. Serologic exam (CBC with platelet, BUN, Crea, Na, K, iCa, LDH, Uric acid, HBsAg, Anti-HCV, SGPT, SGOT, Bilirubins - direct, indirect, total) 2. Chest x-ray (PA and Lateral) - baseline, midcycle, end of the six cycles (if this was used instead of scans) 3. Ultrasound (whole abdomen) - baseline, midcycle, end of the six cycles (if this was used instead of scans) 4. 2D echo with DS vs GLS - baseline and after six cycles of treatment (cardio toxicity of chemotherapy) 5. CT scan - baseline, after three to four cycles of treatment and after completion of six cycles of treatment 6. MRI - baseline, after three to four cycles of treatment and after completion of six cycles of treatment 7. PET - CT - baseline, after three to four cycles of treatment and after completion of six cycles of treatment	None	Diagnostic accuracy, all-cause mortality, DLBCL related mortality, morbidity, false positive, false negative, adverse events, QOL

4. What is the role of Tumor Lysis Syndrome (TLS) prophylaxis in DLBCL?

Population	Intervention	Comparator	Outcomes
Adults with confirmed DLBCL	TLS prophylaxis - Hydration, Allopurinol or Febuxostat (anti-uric acid medication)	Versus no prophylaxis	Adverse events, QOL, overall survival, disease-free survival, mortality-free survival, all-cause mortality, DLBCL related mortality, morbidity

5. What are the treatment strategies for DLBCL among adult population?

Population	Intervention	Comparator	Outcomes
Adults with confirmed DLBCL	Systemic Chemotherapy (R-CHOP and R-EPOCH) 3DCRT versus IMRT versus 2D RT	None	Overall survival, disease-free survival, QOL, mortality-free survival, all-cause mortality, DLBCL related mortality, morbidity

Annex C.3. Post-treatment Evaluation

6. How do we assess or evaluate response to treatment?

Population	Intervention	Comparator	Outcomes
Adults with confirmed DLBCL	Chest x-ray (PA and Lateral) Ultrasound (whole abdomen) CT scan MRI PET-CT	None	QOL, overall survival, disease-free survival, mortality-free survival, all-cause mortality, DLBCL related mortality, morbidity, adverse events

Annex C.4. Source Guideline Content Comparison

DLBCL NCPG Questions and Recommendations		Content Comparison		
		A check (✓) indicates inclusion of the relevant discussion in the guideline.		
		NCCN 2019	**NCCN 2021**	**NICE 2021**
Diagnosis				
What are the mandatory tests to diagnose and subclassify DLBCL (de novo and transformed cases)?	We recommend excisional biopsy, immunohistochemistry (staining for pan-B cell markers such as *CD19, CD20, CD22 and CD79a*) and conventional karyotyping to diagnose DLBCL suspected patients.		✓	
	When the lymph node is not easily accessible for excisional (or incisional) biopsy, we suggest a combination of core biopsy and FNA biopsies in conjunction with appropriate and available ancillary techniques for the differential diagnosis.		✓	
What tests are needed to determine the extent of DLBCL?	We suggest the following diagnostic work-up to determine the extent of the disease among newly diagnosed DLBCL patients: a. Clinical evaluation (history, physical and neurologic examination). b. Chest/abdomen/pelvic CT scan with contrast of quality diagnostics.		✓	.

	c. For patients with neurologic findings on clinical evaluations, lumbar puncture with evaluation of cerebrospinal fluid. d. For patients with high-risk CNS manifestation [including those with greater 1 extra nodal site or certain extra nodal sites (kidney, adrenal gland, testis)] or with neurologic manifestations (re mass effect), offer head or neck CT scan or MRI with contrast of quality diagnostics. e. If CT scan is inconclusive or PET/CT scan is equivocal, offer bone marrow biopsy.			
Treatment and Care				
What essential tests are needed prior to starting treatment and how frequent are these tests monitored during treatment?	We recommend the following pretreatment evaluation among newly diagnosed DLBCL patients: a. Clinical evaluation (*routine*) i. History to identify evidence of comorbidities (heart and renal dysfunction) ii. Physical examination on lymph node-bearing areas (Waldeyer's ring) and size of liver and spleen iii. Neurologic assessment b. Laboratory studies (*routine*) i. Complete blood count with differential count ii. Serum chemistries [electrolytes (i.e., calcium, phosphorous), kidney and liver		✓	✓

	function tests, uric acid, and lactate dehydrogenase] iii. Hepatitis B surface antigen iv. HIV test among high-risk population c. Imaging (*routine and based on clinical evaluation*) i. Left ventricular ejection fraction assessment through echocardiogram			
What is the role of Tumor Lysis Syndrome (TLS) prophylaxis in DLBCL?	We recommend prophylaxis for tumor lysis syndrome whenever available and/or accessible to the patient.	✓		
	We recommend prophylaxis for tumor lysis syndrome whenever available and or accessible to patients. The following prophylactic strategies should be considered: a. Allopurinol b. Febuxostat, if intolerant to Allopurinol c. Rasburicase (*if available*), if with the following conditions: i. Patient with urgent need to initiate therapy in a high bulk patient ii. Situations where adequate may be difficult or impossible iii. Acute renal failure		✓	

What are the treatment strategies for DLBCL among the adult population?	For stages I and II, non-bulky (less than 7.5 cm) cases, we recommend the following as first-line treatment: a. Three cycles of R-CHOP followed by ISRT b. Six cycles of R-CHOP with or without ISRT or four cycles of R-CHOP c. Four cycles of R-CHOP followed by two cycles of Rituximab (If IPI is equal to 0)		✓	
	For bulky (greater than or equal to 7.5 cm) cases, we recommend six cycles of R-CHOP with or without ISRT. If Rituximab is not available, the next best available therapy is CHOP.		✓	
	For stages III and IV, we recommend R-CHOP or offer to enroll the patient in a clinical trial. If Rituximab is not available, the next best available therapy is CHOP.		✓	
	For patients with poor left ventricular function, if available we recommend either the following regimen: a. DA-EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) + Rituximab b. RCDOP (Rituximab, Cyclophosphamide, Liposomal doxorubicin, Vincristine, Prednisone) c. RCEPP (Rituximab, Cyclophosphamide, Etoposide, Prednisone, Procarbazine) d. RCEOP (Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone)		✓	

	e. RGCVP (Rituximab, Gemcitabine, Cyclophosphamide, Vincristine, Prednisolone)			
Post-treatment Evaluation				
How do we assess or evaluate response to treatment?	Based on clinical evaluation, we recommend offering interim imaging through CT scan with contrast of quality diagnostics after the third cycle of treatment to evaluate early response, and after treatment completion to assess treatment success.		✓	✓
	For stage I or II patients with complete response, we recommend following up every three to six months for five years, then yearly or as clinically indicated.		✓	✓
	For stage III or IV patients with complete response, we recommend following up every three to six months for five years, then yearly or as clinically indicated; and imaging on C/A/P/ CT scan with contrast no more often than every six months for two years after completion of treatment, then only as clinically indicated.		✓	✓

Annex D. AGREE II Reporting Checklist (Self Evaluation)

TITLE OF CPG: _____

EVALUATOR: _____ DATE: _____

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
DOMAIN 1. SCOPE AND PURPOSE			
1. THE OVERALL OBJECTIVE(S) OF THE GUIDELINES IS (ARE) SPECIFICALLY DESCRIBED.	□ Health intent □ Expected benefit or outcome □ Target		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
2. THE HEALTH QUESTION(S) COVERED BY THE GUIDELINE IS (ARE) SPECIFICALLY DESCRIBED)	□ Target population □ Intervention or exposure □ Comparisons □ Outcomes □ Health care setting or context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
3. THE POPULATION (PATIENT, PUBLIC, ETC.) TO WHOM THE GUIDELINE IS MEANT TO APPLY IS SPECIFICALLY DESCRIBED.	□ Target population □ Clinical condition □ Severity/stage □ Comorbidities □ Excluded populations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 2. STAKEHOLDER INVOLVEMENT			
4. THE GUIDELINE DEVELOPMENT GROUP INCLUDES INDIVIDUALS FROM ALL RELEVANT PROFESSIONAL GROUPS.	□ Name of participant □ Discipline/content expertise □ Institution □ Geographical location □ A description of the member's role in the guideline development		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
5. THE VIEWS AND PREFERENCES OF THE TARGET POPULATION (PATIENTS, PUBLIC, ETC.) HAVE BEEN SOUGHT.	□ Statement of type of strategy used to capture patient/public views and preferences □ Methods by which preferences and views were sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Outcomes/ information gathered on patient/public information □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations		
6. THE TARGET USERS OF THE GUIDELINE ARE CLEARLY DEFINED.	□ The intended guideline audience □ How the guideline may be used by its target audience		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 3. RIGOUR OF DEVELOPMENT			
7. SYSTEMATIC METHODS WERE USED TO SEARCH FOR EVIDENCE.	□ Named electronic databases or evidence source where the search was performed □ Time periods searched □ Search terms used □ Full search strategy included		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
8. THE CRITERIA FOR SELECTING THE EVIDENCE ARE CLEARLY DESCRIBED.	□ Target population □ Study design □ Comparisons □ Outcomes □ Language □ Context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
9. THE STRENGTHS AND LIMITATIONS OF THE BODY OF EVIDENCE ARE CLEARLY DESCRIBED. TOOLS EXIST THAT CAN FACILITATE THE REPORTING OF THIS CONCEPT.	□ Study design included in body of evidence □ Study methodology limitations □ Appropriateness/ relevance of primary and secondary outcomes considered □ Consistency of results across studies		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Direction of results across studies □ Magnitude of benefit vs magnitude of harm □ Applicability to practice context.		
10, THE METHODS FOR FORMULATING THE RECOMMENDATIONS ARE CLEARLY DESCRIBED. SPECIFY AREAS OF DISAGREEMENTS AND METHODS USED TO RESOLVE THEM.	□ Recommendation development process □ Outcomes of the recommendation development process □ How the process influenced the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
11. THE HEALTH BENEFITS, SIDE EFFECTS, AND RISKS HAVE BEEN CONSIDERED IN FORMULATING THE RECOMMENDATIONS.	□ Supporting data and report of benefits □ Supporting data and report of harms/side effects/ risks □ Reporting of the balance/trade-off between benefits and harms/side effects/risks □ Recommendations reflect considerations of both benefits and harms/side effects/risks		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
12. THERE IS AN EXPLICIT LINK BETWEEN THE RECOMMENDATIONS AND THE SUPPORTING EVIDENCE.	□ How the guideline development group linked and used the evidence to inform recommendations. □ Link between each recommendation and key evidence □ Link between recommendations and evidence summaries/or evidence tables in the results section of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
13. THE GUIDELINE HAS BEEN EXTERNALLY REVIEWED BY EXPERTS PRIOR TO ITS PUBLICATION.	□ Purpose and intent of the external review □ Methods taken to undertake the external review		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Description of the external reviewers □ Outcomes/information gathered from the external review □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		Comments:
14. A PROCEDURE FOR UPDATING THE GUIDELINE IS PROVIDED.	□ A statement that the guideline will be updated □ Explicit time interval or explicit criteria to guide decisions about when an update will occur □ Methodology for the updating procedure		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 4. CLARITY OF PRESENTATION			
15. THE RECOMMENDATIONS ARE SPECIFIC AND UNAMBIGUOUS.	□ A statement of the recommended action □ Intent or purpose of the recommended action □ Relevant population □ Caveats or qualifying statements, if relevant □ If there is uncertainty about the best care option, the uncertainty should be stated in the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
16. THE DIFFERENT OPTIONS FOR MANAGEMENT OF THE CONDITION OR HEALTH ISSUE ARE CLEARLY PRESENTED.	□ Description of management options □ Population or clinical situation most appropriate to each option		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
17. KEY RECOMMENDATIONS ARE EASILY IDENTIFIABLE.	□ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms □ Specific recommendations grouped together in one section		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 5. APPLICABILITY			
18. THE GUIDELINE DESCRIBES FACILITATORS AND BARRIERS TO ITS APPLICATION.	□ Types of facilitators and barriers that were considered □ Method by which information regarding the facilitators and barriers to implementing recommendations were sought. □ Information/ description of the types of facilitators and barriers that emerged from the injury □ How the information influenced the guideline development process and/or formation of the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
19. THE GUIDELINE PROVIDES ADVICE AND/OR TOOLS ON HOW THE RECOMMENDATIONS CAN BE PUT INTO PRACTICE.	□ Additional materials to support the implementation		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
20. THE POTENTIAL SOURCE IMPLICATIONS OF APPLYING THE RECOMMENDATIONS HAVE BEEN CONSIDERED.	□ Types of cost information that were considered □ Methods by which the cost information was sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Information/ description of the cost information that emerged from the inquiry □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		
21. THE GUIDELINE PRESENTS MONITORING AND/OR AUDITING CRITERIA.	□ Criteria to assess guideline implementation or adherence to recommendations □ Criteria for assessing impact of implementing the recommendations □ Advice on the frequency and interval of measurement □ Operational definitions of how the criteria should be measured.		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 6. EDITORIAL INDEPENDENCE			
22. THE VIEWS OF THE FUNDING BODY HAVE NOT INFLUENCED THE CONTENT OF THE GUIDELINE.	□ The name of the funding body or source of funding □ A statement that the funding body did not influence the content of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
23. COMPETING INTERESTS OF GUIDELINE DEVELOPMENT GROUP MEMBERS HAVE BEEN RECORDED AND ADDRESSESD.	□ Types of competing interests considered □ Methods by which potential competing interests were sought □ a description of the competing interests □ How the competing interests influenced the guideline process and		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments: