BLOOD RESEARCH
VOLUME 57 · NUMBER S1
April 2022
REVIEW ARTICLE

Staging and response assessment of lymphoma: a brief review of the Lugano classification and the role of FDG-PET/CT

Kwai Han Yoo

Division of Hematology, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Korea

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2022.2022055
Blood Res 2022;57:S75-S78.

Received on March 1, 2022
Revised on April 6, 2022
Accepted on April 6, 2022

Correspondence to
Kwai Han Yoo, M.D.
Division of Hematology, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, 21, Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea
E-mail: dr.kyleu@gmail.com

Abstract

The accurate assessment of initial disease status and therapeutic responses is critical to the optimal management of patients with lymphoma. Currently, staging and treatment response evaluation for lymphoma has been standardized into the Lugano classification. Lugano classification incorporates positron emission tomography (PET) into the existing response criteria, and response assessment using FDG-PET/CT has been proven to predict the prognosis in various lymphoma subtypes effectively. We will briefly review the current staging and response evaluation system and explore the role of functional imaging in the field of lymphoma.

Key Words Lymphoma, Staging, Response assessment, Lugano classification, FDG-PET/CT

INTRODUCTION

Lymphoma is the most common hematological malignancy and is divided into more than 80 subtypes by the latest World Health Organization classification revised in 2016 [1]. In South Korea, lymphoma accounts for 2.3% of all newly diagnosed cancers (according to the annual report of cancer statistics in Korea), and approximately 5,216 new cases of non-Hodgkin lymphoma (NHL) and 299 new cases of Hodgkin lymphoma (HL) were diagnosed in 2018 [2].

The accurate assessment of initial disease status and therapeutic responses is critical to the optimal management of patients with lymphoma. Currently, staging of lymphoma and evaluation of treatment response are primarily performed according to the Lugano 2014 classification, and the importance of functional imaging such as 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) is increasingly being emphasized [3]. In this article, we will review Lugano classification and the role of FDG-PET/CT in the management of lymphoma.

THE LUGANO CLASSIFICATION

In 1999, the National Cancer Institute Working Group established the first universally accepted response criteria for both NHL and HL [4], and revised in 2007 by the International Working Group to incorporate PET and bone marrow immunohistochemistry and flow cytometry [5]. As the experience of FDG-PET/CT has been gradually accumulated, FDG-PET/CT has been recognized for its definite usefulness in the evaluation of lymphoma [6]. Lymphoma staging is currently based upon the Lugano 2014 classification formulated at the 11th and 12th International Conference on Malignant Lymphomas in Lugano, Switzerland.

Initial evaluation and staging

For accurate diagnosis of various subtypes of lymphoma, an incisional or excisional biopsy is preferred to provide adequate tissue for morphology, immunohistochemistry, and additional molecular study [1]. However, a core-needle biopsy can be considered when an excisional biopsy is impossible [7].

FDG-PET/CT scanning has become the standard for staging and assessment of response in HL and FDG-avid NHL

subtypes [8, 9]. A contrast-enhanced CT scan is recommended for FDG non-avid histologies and is also recommended if measuring nodes is essential or for radiotherapy planning. For patients staged with FDG-PET/CT, focal uptake in nodal and extranodal sites is considered involvement with lymphoma [10].

If an FDG-PET/CT is performed, a bone marrow biopsy (BMB) is no longer indicated for HL [11]. A BMB is only needed for diffuse large B-cell lymphoma (DLBCL) if the FDG-PET/CT is negative and identifying discordant histology is important for patient management [12]. All other lymphoma histologies are insufficient to change the standard practice, and unilateral BMB is recommended.

Combining the above, a modification of the Ann Arbor classification is recommended (Table 1). Suffixes A and B indicating the presence of symptoms of lymphoma are only required for HL, and the designation X for bulky disease is no longer necessary.

Response assessment and follow-up evaluation

Interim and end-of-treatment (EOT) assessment with FDG-PET/CT is recommended with Deauville 5-point scale (Table 2), while CT-based response is preferred for histologies with low or variable FDG-avidity [13]. EOT scans are generally performed 6–8 weeks following completion of treatment, but a different time point may be needed for regimens containing various immunological agents currently used. Metabolic response criteria using Deauville 5-point scale is given in Table 3.

Once EOT response has been assessed and achieved complete response, further imaging studies should be performed carefully and triggered by clinical indications. Surveillance scans after remission are discouraged, especially for DLBCL and HL [3, 5].

Table 1. A modified Ann Arbor staging system.

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

CURRENT ROLE OF FDG-PET/CT IN THE MANAGEMENT OF LYMPHOMA AND FUTURE DIRECTION

Baseline FDG-PET/CT affects clinical prognostication of most subtypes of lymphoma including DLBCL, peripheral T-cell lymphoma (PTCL), follicular lymphoma (FL), and HL [6, 14-16]. In the staging of FDG-avid subtypes, FDG-PET/CT is the preferred modality for staging than CT, especially for identifying extranodal sites [10]. FDG-PET/CT removes the need for BMB in most patients of DLBCL and HL, and it allows for mapping of initial disease sites for accurate response assessment [17]. For patients with PTCL, FDG-PET/CT identifies more disease sites and usually upstages diagnosis compared with CT, but PET-induced stage alteration rarely changes treatment strategies because most affected patients have advanced disease [18].

Table 2. The Deauville 5-point scale.

Score	Definition
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Moderately increased uptake compared to the liver
5	Markedly increased uptake compared to the liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Table 3. Metabolic response criteria using Deauville score (adapted from Lugano classification).

Response categories	FDG-PET/CT-based response
Complete metabolic response	Scores 1, 2 and 3 in nodal or extranodal sites with or without a residual mass using the five-point scale
Partial metabolic response	Score 4 or 5, with visually reduced uptake compared with baseline and residual mass(es) of any size - *At interim these findings may suggest responding disease; at end of treatment these findings indicate residual metabolic disease* - *Bone marrow: residual marrow uptake > normal marrow but reduced compared with baseline (diffuse changes from chemotherapy allowed)*
No metabolic response	Score 4 or 5 with no significant change in uptake from baseline (at interim or end of treatment)
Progressive metabolic disease	Score 4 or 5 with an increase in uptake from baseline and/or new FDG-avid foci consistent with lymphoma (at interim or end of treatment)

The predictive value of interim FDG-PET/CT has been evaluated in early or advanced-stage HL, DLBCL, PTCL, extranodal natural killer/T-cell lymphoma, and primary mediastinal B-cell lymphoma (PMBCL) [19-21]. Most previous studies have emphasized the role of interim FDG-PET/CT for confirming early response during first-line chemotherapy treatment, especially in HL [21], but an increased number of reports have recently been published focusing on relapsed or refractory disease of HL and NHL to predict the outcome of salvage treatment [19, 22].

FDG-PET/CT provides quantitative information on tumor burden. Several studies suggest that metabolic tumor volume (MTV) and tumor lesion glycolysis (TLG) are associated with worse prognosis in high-tumor burden DLBCL, PTCL, and FL [23-25]. In patients with PMBCL, TLG was an independent predictor of worse progression-free survival [26]. MTV could have an important role in developing risk-adapted approaches in NHL, and cooperative efforts for standardization of MTV measurement is warranted.

Most recently, research on PET-based quantitative evaluation of cancer using artificial intelligence (AI) and deep learning has been actively conducted [27, 28]. Multiple studies suggested AI could enhance the characterization and quantification of tumors and predict treatment response and risk stratification of recurrence [29]. Although it is still challenging to apply AI-based procedures routinely in clinical practice, it is expected that experiences and data will be gradually accumulated, and more effective clinical application of FDG-PET/CT on lymphoma will be achieved.

CONCLUSIONS

Accurate pretreatment staging and evaluation of treatment response are critical for establishing a treatment strategy for lymphoma. Lymphoma staging and response assessment systems have evolved with advances in radiologic techniques and Lugano classification has been widely used for most subtypes NHL and HL by combining FDG-PET/CT. It is expected that the more sophisticated application of functional imaging techniques along with the development of various biologic therapeutic agents will contribute to improving the survival rate of lymphoma patients.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
2. Hong S, Won YJ, Lee JJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2018. Cancer Res Treat 2021;53:301-15.
3. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.
4. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.
5. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.
6. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014;32:3048-58.
7. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol 2004;22:3046-52.
8. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007;110:3507-16.
9. Hosein PJ, Lossos IS. The evolving role of F-FDG PET scans in patients with aggressive non-Hodgkin's lymphoma. European J Clin Med Oncol 2010;2:131-8.
10. Cheson BD. Role of functional imaging in the management of lymphoma. J Clin Oncol 2011;29:1844-54.
11. El-Galaly TC, d'Amore F, Mylam KJ, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. J Clin Oncol 2012;30:4508-14.
12. Khan AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood 2013;122:61-7.
13. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010;37:1824-33.
14. Frood R, Burton C, Tsoumpas C, et al. Baseline PET/CT imaging parameters for prediction of treatment outcome in Hodgkin and diffuse large B cell lymphoma: a systematic review. Eur J Nucl Med Mol Imaging 2021;48:3198-220.
15. Nakajima R, Moskowitz AJ, Michaud L, et al. Baseline FDG-PET/CT detects bone marrow involvement in follicular lymphoma and provides relevant prognostic information. Blood Adv 2020;4:1812-23.
16. Mehta-Shah N, Ito K, Bantilan K, et al. Baseline and interim functional imaging with PET effectively risk stratifies patients with peripheral T-cell lymphoma. Blood Adv 2019;3:187-97.
17. Cheson BD, Meignan M. Current role of functional imaging in the management of lymphoma. Curr Oncol Rep 2021;23:144.
18. Casulo C, Schöder H, Feeney J, et al. 18F-fluorodeoxyglucose positron emission tomography in the staging and prognosis of T cell lymphoma. Leuk Lymphoma 2013;54:2163-7.
19. Milgrom SA, Rechner L, Berthelsen A. The optimal use of PET/CT in the management of lymphoma patients. Br J Radiol 2021;94:20210470.

20. Susanibar-Adaniya S, Barta SK. 2021 update on diffuse large B cell lymphoma: a review of current data and potential applications on risk stratification and management. Am J Hematol 2021;96:617-29.
21. Barrington SF, Trotman J. The role of PET in the first-line treatment of the most common subtypes of non-Hodgkin lymphoma. Lancet Haematol 2021;8:e80-93.
22. Phillips EH, Iype R, Wirth A. PET-guided treatment for personalised therapy of Hodgkin lymphoma and aggressive non-Hodgkin lymphoma. Br J Radiol 2021;94:20210576.
23. Jiang C, Ding C, Xu J, et al. Will baseline total lesion glycolysis play a role in improving the prognostic value of the NCCN-IPI in primary gastric diffuse large B-cell lymphoma patients treated with the R-CHOP regimen? Clin Nucl Med 2021;46:1-7.
24. Feng X, Wen X, Li L, et al. Baseline total metabolic tumor volume and total lesion glycolysis measured on 18F-FDG PET-CT predict outcomes in T-cell lymphoblastic lymphoma. Cancer Res Treat 2021;53:837-46.
25. Guo B, Tan X, Ke Q, Cen H. Prognostic value of baseline metabolic tumor volume and total lesion glycolysis in patients with lymphoma: a meta-analysis. PLoS One 2019;14:e0210224.
26. Ceriani L, Martelli M, Zinzani PL, et al. Utility of baseline 18FDG-PET/CT functional parameters in defining prognosis of primary mediastinal (thymic) large B-cell lymphoma. Blood 2015;126:950-6.
27. Sadaghiani MS, Rowe SP, Sheikhbahaei S. Applications of artificial intelligence in oncologic 18F-FDG PET/CT imaging: a systematic review. Ann Transl Med 2021;9:823.
28. Hasani N, Paravastu SS, Farhadi F, et al. Artificial intelligence in lymphoma PET imaging: a scoping review (current trends and future directions). PET Clin 2022;17:145-74.
29. Li W, Liu H, Cheng F, Li Y, Li S, Yan J. Artificial intelligence applications for oncological positron emission tomography imaging. Eur J Radiol 2021;134:109448.