Clinical and Biological Prognostic Factors in Follicular Lymphoma Patients During Treatment

Ádám Jóna (jadam1@unideb.hu)
University of Debrecen

Anna Kenyeres
University of Debrecen

Sándor Bama
Scanomed Ltd.

Árpád Illés
University of Debrecen

Zsófia Simon
University of Debrecen

Research Article

Keywords: follicular lymphoma, PET/CT, interim PET, lymphocyte/monocyte ratio, prognostic marker

DOI: https://doi.org/10.21203/rs.3.rs-275643/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

**Introduction:** Follicular lymphoma (FL) is an indolent yet heterogeneous B-cell lymphoproliferative disorder. Most people respond to treatment well. However, a particular group of patients has a poor prognosis, and these patients are difficult to define.

**Patients and methods:** We retrospectively analyzed FL patients treated at the University of Debrecen in the past 20 years. We investigated prognostic factors that may influence the survival of FL patients.

**Results:** We found a standardized uptake value (SUV)max cut-off value of 9.85 at the staging PET/CT to significantly separate FL patients’ progression-free survival (PFS) (p=0.0003, HR: 0.2560, 95%CI: 0.1232-0.5318). Lymphocyte/monocyte (Ly/Mo) ratio of 3.45 drawn at diagnosis also significantly predicted PFS (p=0.0324, HR: 1.806, 95% CI: 1.051-3.104). Combining patients’ with staging SUVmax >9.85 and Ly/Mo < 3.45 a high-risk group of FL patients can be identified (p<0.0001, HR: 0.1033, 95% CI: 0.03719-0.2868). Similarly, a significant difference was shown with a SUVmax cut-off of 3.15 at the interim PET/CT (p<0.0001, HR: 0.1535, 95% CI: 0.06329-0.3720). Combining patients with staging SUVmax >9.85 and interim SUVmax >3.15, a high-risk group of FL patients can be identified (p<0.0001, HR: 0.1037, 95% CI: 0.03811-0.2824). The PFS difference is translated into overall survival advantage (p=0.0506, HR: 0.1187, 95% CI: 0.01401-1.005).

**Discussion:** Biological prognostic factors, such as the Ly/Mo ratio, may improve the prognostic assessment of staging PET/CT. Nevertheless, PFS difference is translated into OS when using a combination of staging and interim SUVmax. We consider investigating additional biological prognostic factors while currently highlighting PET/CT’s role in FL.

Introduction

Follicular lymphoma (FL) is an indolent, germinal center B-cell-derived lymphoproliferative disease. [1] In general, FL is associated with the undue function of the proto-oncogene BCL2, which is activated by chromosome translocation of t(14;18) (q32; q21). [2] FL is the most common non-Hodgkin lymphoma (NHL) in the Western world [3], representing 35% of all NHLs.

FL is a biologically and clinically heterogeneous disease with a wide variation in the outcomes of individual patients. Results for FL treatment have improved significantly, thanks to the introduction of anti-CD20 antibody rituximab, median overall survival (OS) of FL is approaching 20 years [4], but most patients eventually relapse. The ability to provide individualized treatment based on risk assessment of individual patients is the subject of ongoing research.

Classically, histological grade, tumor mass, Follicular Lymphoma International Prognostic Index (FLIPI) 1 (involvement of > 4 lymph node regions, elevated LDH, > 60 years of age, advanced stage and < 120 g/L hemoglobin) and − 2 (elevated beta-2 microglobulin (B2M), largest diameter lymph node greater than 6 cm, bone marrow involvement, < 120 g / L hemoglobin, > 60 years of age) are the parameters by which
low- and high-risk patients are distinguished. [5] Several reports confirmed the unfavorable survival of FL patients who progress early after stopping treatment. Twenty percent of patients are expected to progress within 24 months. [6–8] Unfortunately, the range of these patients cannot be determined in advance. Hence, we need to precisely predict patients’ outcomes.

**Patients And Methods**

We retrospectively investigated our FL patients’ prognostic factors treated between 2000 and 2020 at the University of Debrecen (UD), Department of Hematology. Factors that may have influenced survival: histology, age, stage, sex, staging-, interim- and restaging standardized uptake value (SUV) max, presence or absence of B symptoms, bone marrow involvement, ECOG performance status, hemoglobin (Hgb), lactate dehydrogenase (LDH), B2M, absolute lymphocyte (Ly), and monocyte (Mo) count, lymphocyte/monocyte (Ly/Mo) ratio, the progression of disease within 24 months (POD24). POD24 was calculated from the time of diagnosis until progression.

This retrospective analysis was approved by The Regional and Institutional Research Ethics Committee of the University of Debrecen.

The patients were treated according to the current guideline of the Hungarian Society of Hematology and Transfusion. The patients consented before treatment initiation to collect and publish their data retrospectively according to the Declaration of Helsinki. PET/CT was used routinely as an imaging modality at the UD since 2008. However, it was not routine in the interim and restaging setting. A staging PET/CT was done for every patient after a histological diagnosis of disease, unless there was a clinical urgency or the patient was treated primarily in another institution with no access to PET/CT scans. Interim PET/CT was performed after 3 cycles of immune-chemotherapy, while restaging PET/CT was done after 4–6 weeks of completion of induction treatment.

Patient outcome was analyzed by progression-free survival (PFS) and overall survival (OS). PFS was calculated from diagnosis to June 2020, progression, histological transformation, or death, while OS was calculated from diagnosis to June 2020 or death. Survival was estimated based on the Kaplan-Meier method. Factors that could affect survival were evaluated based on a multivariable Cox regression model with a stepwise backward variable selection approach to obtain hazard ratio (HR). Comparison of the survival curves was based on the Log-rank test.

**Results**

We investigated 211 FL patients with a median age of 53 years. The majority of them had B symptoms. Grade 1 and 2 histology occurred in about ⅔ of the cases. The majority of the patients were diagnosed with advanced-stage disease. POD24 cases were found in less than ⅓ of the cases. Out of FL patients diagnosed since 2008, we found 115 accessible staging PET/CT-s. Sixty-five of them had an interim, while 80 had a restaging scan. First line treatment was dominated by anti-CD20 antibody, rituximab,
whereas the major chemotherapy backbone was –CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)(-like), -CVP (cyclophosphamide, vincristine, prednisolone), or bendamustine. Table 1.

Age, staging, interim PET/CT, ECOG performance status, Hgb, LDH, Ly, Mo, and Ly/ Mo ratio affected PFS. The interim PET/CT, Ly, Mo were excluded because they are related to another variable. We put the rest into a multivariable COX regression; staging PET/CT and Ly/ Mo ratio remain an independent prognostic factor for PFS. Table 2.

A total of 115 patients had PET/CT as staging imaging modality since 2008. We investigated SUVmax values, and with the ROC curve, we found a cut-off value of 9.85 (range: 5.6 – 28.9) to divorce survival significantly. When illustrating the patients' PFS, a significant difference was found when using the defined SUVmax cut-off value (p=0.0003, HR: 0.2560, 95% CI: 0.1232-0.5318). The median PFS of FL patients with SUVmax> 9.85 was 51 months, while median PFS with SUVmax <= 9.85 was not met. Five-year PFS was 85.29 vs. 48.25%. When presenting these patients’ overall survival, the difference is not significant (5-year OS: 96.87 vs. 85.73%). Figure 1. Histology was done from the most accessible site since the histology result is needed to order a PET/CT imaging. Patients with a relatively high staging SUVmax or with grade 3a histology received R-CHOP protocol.

A total of 169 patients had an accessible blood count in the medical record system. The cut-off value for Ly/ Mo was found to be 3.45 with the ROC curve. When illustrating the PFS of these patients using the defined value, we found a statistically significant difference (p=0.0324, HR: 1.806, 95% CI: 1.051-3.104). Median PFS of FL patients with Ly/Mo ratio <3.45 was 92 months, while median PFS with Ly/Mo > 3.45 was not met. Five-year PFS was 74.41 vs. 52.02%. When presenting these patients' overall survival, the previously described difference was did not convert into a significant overall survival difference (p=0.0390, HR: 2.838, 95% CI: 1.054-7.644). Median survivals were not met, while 5-year PFS was 94.98 vs. 83.38%. Figure 2. Combining patients with staging SUVmax >9.85 and Ly/Mo < 3.45 a high-risk group of FL patients can be identified (p<0.0001, HR: 0.1033, 95% CI: 0.03719-0.2868). Median survival was 42 months for the high-risk group with SUVmax >9.85 and Ly/Mo < 3.45, while the median survival of the rest of the patients was not met. Five-year PFS was 86.16 vs. 38.54%. Figure 3.

A total of 65 patients had interim PET/CT scans. A SUVmax of 3.15 was identified as cut-off by the ROC curve. A significant difference was found when illustrating the patients' progression-free survival when using the defined SUVmax cut-off value (p<0.0001, HR: 0.1535, 95% CI: 0.06329-0.3720). Median survival was 32 months for those FL patients, whose interim PET/CT had a SUVmax of >3.15. The median survival of patients with interim SUVmax <=3.15 was not met. Five-year PFS was 83.52 vs. 34.86%. When presenting the overall survival of these patients, the difference is not significant. (5-year PFS: 95.23 vs. 86.16%) Figure 4.

Combining patients with staging SUVmax >9.85 and interim SUVmax >3.15, a high-risk group of FL patients can be identified again (p<0.0001, HR: 0.1037, 95% CI: 0.03811-0.2824). Median PFS of FL patients whose staging PET/CT had a SUVmax of >9.85 and SUVmax of the interim PET/CT >3.15 was 21 months, while the median survival of the rest of the patients was not met. Five-year PFS was 81.035
vs. 25.45%. The PFS difference is translated into OS disadvantage (p=0.0506, HR: 0.1187, 95% CI: 0.01401-1.005). Five-year PFS was 95.00 vs. 81.20%. **Figure 5.**

When we combine all staging-, interim SUVmax and Ly/Mo ratio we cannot further improve PFS (p<0.0001, HR: 0.08303, 95% CI: 0.02492-0.2766, median PFS: 32 months vs. not met, 5-year PFS: 82.31 vs. 25.71%) and OS significance rate (p=0.1059, HR: 0.1184, 95% CI: 0.008919-1.572, 5-year OS: 95.00 vs. 84.41%). (Data not shown)

Restaging SUVmax defined PFS at a cut-off value of 2.45 determined by the ROC curve (p=0.0175, HR: 0.3200, 95% CI: 0.1250-0.8192, median PFS: 92 months vs. not met, 5-year PFS: 74.00 vs. 50.94%). Data for OS was not significant again (p=0.4874, HR: 0.4929, 95% CI: 0.06693-3.630, 5-year PFS: 91.78 vs. 86.66%). (Data not shown)

**Discussion**

The weakness of FLIPI is that it has been determined on the one hand using retrospective data. On the other hand, it does not define a treatment indication and, like International Prognostic Index (IPI), it represents few high-risk patients. FLIPI2 is designed to protect against all this. Treatment is still determined based on high tumor mass according to the criteria of the Groupe d'Etude des Lymphomes Folliculaires (GELF) [9] or the British National Lymphoma Investigation (BNLI) [10, 11].

Initial total metabolic tumor volume (TMTV) measured by PET/CT was strongly correlated with survival in FL patients who received R-CHOP without maintenance treatment. [12] Patients with TMTV > 510 cm3 had a significantly less favorable 33% 5-year PFS compared with 65% 5-year PFS in patients with TMTV < 510 cm3. The 5-year overall survival (OS) was 85% and 95%, respectively. We found that staging SUVmax was prognostic for PFS with a cut-off of 9.85 based on 115 FL patients' data. The survival advantage, however, did not translate into significant OS differences. Our 5-year PFS (85.29 vs. 48.25%) and OS (96.87 vs. 85.73%) results with staging SUVmax were similar to that found with TMTV.

A low lymphocyte count is an adverse prognostic factor not only in Hodgkin lymphoma (HL) [13] but in FL, also [14] and may relate to the patient's immunity. In contrast, monocyte count could relate to the tumor microenvironment. [15] Elevated monocyte count was associated with a poor prognosis. Ly/Mo count is also reported to be a prognostic factor in HL. [16, 17] In our multivariate analysis Ly/Mo ratio was prognostic in our FL dataset. The cut-off value of 3.45 was similar to that found in our HL population [18] and found in an Italian [19] and Hong Kong FL dataset. [20] Ly/Mo ratio is not standardized since the results are scattered, however when combined staging SUVmax with Ly/Mo ratio p-value improved both for PFS and OS. Further, larger studies are warranted to specify prognostic value of Ly/Mo ratio in FL.

The PET/CT is a standard imaging method for response evaluation in FDG-avid lymphomas, including FL. However, prognostic evaluation in FL by PET/CT is not widely established. In a study published in 2019, a survey of 33 (!) FL patients found that interim PET/CT done after 3 or 4 cycles of first-line treatment were predictive of progression-free survival (PFS). [21] A meta-analysis published in 2016
found one trial that reported a positive correlation between positive or negative interim PET/CT results and PFS, while two studies reported a negative correlation. [22] Our results confirm a positive correlation. The interim PET/CT scan of 65 FL patients, performed after three cycles of immunochemotherapy, and a cut-off of 3.15 SUVmax showed significant PFS survival benefit. However, the difference was not significant in terms of OS, which may be explained by extensive and effective relapsing treatment options. [23] A recent paper, published in 2019, reported 84 FL patients, of whom 59 had a baseline and 24 an interim PET/CT scan. Similarly to our results, they found a positive correlation between the baseline SUVmax value of 10.44 and PFS. However, survival difference was not significant in terms of OS. Interim PET/CT results interpreting them as “positive /negative”, “Deauville score 1-3 and 4-5” and “ΔSUVmax (change of SUVmax from baseline to interim point)” were neither prognostic for PFS nor OS. [24]

Nevertheless, when we combined staging and interim SUVmax, a patient group with a significantly poor prognosis could have been identified. The significant survival disadvantage in PFS is translated into OS difference, also. Half of these patients progress within 21 months, determining POD24 patients after three cycles (and practically three months) of treatment. POD 24 also translates to OS disadvantage. We believe this is an unmet medical need. Patients belonging to this group should change therapy with a more aggressive therapeutic approach – if possible – (compared to the indolent clinical characteristic of FL) after getting an unfavorable interim PET/CT scan result. It would be fortunate to predict even earlier these adverse cases, possible at the time of diagnosis. Therefore, these patients could get more aggressive treatment or vice versa: should the good prognostic group get more “permissive” therapy e.g., leaving maintenance therapy at the time of ongoing COVID pandemic and thus moderating B cell depletion [25] or just because the patient requires continuous granulocyte colony stimulating factor support?

Restaging PET/CT results are reported in several ways to predict PFS. PET/CT done three months after completion of induction treatment was also an independent prognostic factor. [26, 27] A meta-analysis of large multi-center trials verified in 2014 that a negative PET/CT done after six cycles of induction treatment was prognostic for both PFS and OS. [28] Our results of restaging PET/CT scans were also prognostic for PFS at a cut of 2.45 SUVmax. However, the results were not significant again in terms of OS.

Based on these, we believe that although biological prognostic factors, such as the Ly/ Mo ratio, are essential because they may improve the prognostic assessment of staging PET/CT. We can demonstrate the difference in overall survival using a combination of staging and interim SUVmax. Besides, this can provide more significant help than the individual use of staging or interim SUVmax. For all these reasons, we consider it necessary to investigate additional biological prognostic factors while currently highlighting PET/CT’ s role in FL.

Declarations
Acknowledgement:
The authors thank Katalin Hódosi for statistical support.

Statement of Ethics:
This retrospective analysis was approved by the The Regional and Institutional Research Ethics Committee of the University of Debrecen.

Informed consent and consent for publication:
The patients consented before treatment initiation to collect and publish their data retrospectively according to the Declaration of Helsinki.

Availability of data:
All data generated or analyzed during this study are anonymized and included in this published article [and its supplementary information files]

Competing interest:
The authors have no conflicts of interest to declare.

Author’s contribution:
ÁJ analyzed data and wrote the manuscript, AK collected and analyzed data, SB collected data and contributed with essential examinations to the study, ÁI analyzed data and approved the final manuscript, ZS analyzed data, critically analyzed and accepted the final manuscript

All authors read and approved the manuscript.

Funding:
ÁJ was Supported by the ÚNKP-20-4 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund.

References
1. Linet MS, Vajdic CM, Morton LM, de Roos AJ, Skibola CF, Boffetta P, Cerhan JR, Flowers CR, de Sanjose S, Monnereau A, Cocco P, Kelly JL, Smith AG, Weisenburger DD, Clarke CA, Blair A, Bernstein L, Zheng T, Miligi L, Clavel J, Benavente Y, Chiu BC. Medical history, lifestyle, family history, and occupational risk factors for follicular lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014;2014(48):26-40. doi: 10.1093/jncimonographs/lgu006.

2. Ambinder AJ, Shenoy PJ, Malik N, Maggioncalda A, Nastoupil LJ, Flowers CR. Exploring risk factors for follicular lymphoma. Adv Hematol. 2012;2012:626035.(doi):10.1155/2012/626035. Epub 2012 Sep 18.

3. Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, Patmore R, Jack A, Roman E. Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. Br J Cancer. 2015;112(9):1575-84. doi: 10.038/bjc.2015.94. Epub Mar 24.

4. Tan D, Horning SJ, Hoppe RT, Levy R, Rosenberg SA, Sigal BM, Warnke RA, Natkunam Y, Han SS, Yuen A, Plevritis SK, Advani RH. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. Blood. 2013;122(6):981-7. doi: 10.1182/blood-2013-03-491514. Epub 2013 Jun 18.

5. Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, Pro B, Pileri S, Pulsoni A, Soubeyran P, Cortelazzo S, Martinelli G, Martelli M, Rigacci L, Arcaini L, Di Raimondo F, Merli F, Sabattini E, McLaughlin P, Solal-Céligny P. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol. 2009;27(27):4555-62. doi: 10.1200/JCO.2008.21.3991. Epub 2009 Aug 3.

6. Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR, Hainsworth JD, Maurer MJ, Cerhan JR, Link BK, Zelenetz AD, Friedberg JW. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516-22. doi: 10.1200/JCO.2014.59.7534. Epub 2015 Jun 29.

7. Maurer MJ, Bachy E, Ghesquières H, Ansell SM, Nowakowski GS, Thompson CA, Inwards DJ, Allmer C, Chassagne-Clément C, Nicolas-Virelizier E, Sebba C, Lebras L, Sarkozy C, Macon WR, Feldman AL, Syrbiu SI, Traverse-Glehan A, Coiffier B, Slager SL, Weiner GJ, Witzig TE, Habermann TM, Salles G, Cerhan JR, Link BK. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. Am J Hematol. 2016;91(11):1096-101. doi: 10.02/ajh.24492. Epub 2016 Sep 3.

8. Shi Q, Flowers CR, Hiddemann W, Marcus R, Herold M, Hagenbeek A, Kimby E, Hochster H, Vitolo U, Peterson BA, Gyan E, Ghielmini M, Nielsen T, De Bedout S, Fu T, Valente N, Fowler NH, Hoster E, Ladetto M, Morschhauser F, Zucca E, Salles G, Sargent DJ. Thirty-Month Complete Response as a Surrogate End Point in First-Line Follicular Lymphoma Therapy: An Individual Patient-Level Analysis of Multiple Randomized Trials. J Clin Oncol. 2017;35(5):552-60. doi: 10.1200/JCO.2016.70.8651. Epub 2016 Dec 28.
9. Brice P, Bastion Y, Lepage E, Brousse N, Haøoun C, Moreau P, Straetmans N, Tilly H, Tabah I, Solal-Cœligny P. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 1997;15(3):1110-7. doi: 10.200/JCO.997.15.3..

10. Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA, Marcus RE, Jelliffe A, Vaughan G, Hudson, Linch DC. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003;362(9383):516-22. doi: 10.1016/s0140-6736(03)14110-4.

11. Ardeshna KM, Qian W, Smith P, Braganca N, Lowry L, Patrick P, Warden J, Stevens L, Pocock CF, Miall F, Cunningham D, Davies J, Jack A, Stephens R, Walewski J, Ferhanoglu B, Bradstock K, Linch DC. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol. 2014;15(4):424-35. doi: 10.1016/S470-2045(14)70027-0. Epub 2014 Mar 4.

12. Meignan M, Cottereau AS, Versari A, Chartier L, Dupuis J, Boussetta S, Grassi I, Casasnovas RO, Haïoun C, Tilly H, Tarantino V, Dubreuil J, Federico M, Salles G, Luminari S, Trotman J. Baseline Metabolic Tumor Volume Predicts Outcome in High-Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies. J Clin Oncol. 2016;34(30):3618-26. doi: 10.1200/JCO.2016.66.9440. Epub 2016 Sep 30.

13. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998;339(21):1506-14. doi: 10.056/NEJM199811193392104.

14. Siddiqui M, Ristow K, Markovic SN, Witzig TE, Habermann TM, Colgan JP, Inwards DJ, White WL, Ansell SM, Micallef IN, Johnston PB, Call TG, Porrata LF. Absolute lymphocyte count predicts overall survival in follicular lymphomas. Br J Haematol. 2006;134(6):596-601. doi: 10.1111/j.365-2141.006.06232.x. Epub 2006 Aug 1.

15. Watanabe R, Tomita N, Kishimoto K, Koyama S, Ogusa E, Ishii Y, Miyashita K, Matsuura S, Fujisawa S, Hattori Y, Takasaki H, Fujita A, Ohshima R, Kuwabara H, Hashimoto C, Fujimaki K, Sakai R, Ishigatsubo Y. Absolute monocyte count in follicular lymphoma patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Leuk Res. 2013;37(10):1208-12. doi: 10.016/j.leukres.2013.07.015. Epub Aug 5.

16. Koh YW, Kang HJ, Park C, Yoon DH, Kim S, Suh C, Go H, Kim JE, Kim CW, Huh J. The ratio of the absolute lymphocyte count to the absolute monocyte count is associated with prognosis in Hodgkin's lymphoma: correlation with tumor-associated macrophages. Oncologist. 2012;17(6):871-80. doi: 10.1634/theoncologist.2012-0034. Epub 2012 May 15.

17. Porrata LF, Ristow K, Colgan JP, Habermann TM, Witzig TE, Inwards DJ, Ansell SM, Micallef IN, Johnston PB, Nowakowski GS, Thompson C, Markovic SN. Peripheral blood lymphocyte/monocyte ratio at diagnosis and survival in classical Hodgkin's lymphoma. Haematologica. 2012;97(2):262-9. doi: 10.3324/haematol.2011.050138. Epub 2011 Oct 11.
18. Simon Z, Barna S, Miltenyi Z, Husi K, Magyari F, Jona A, Garai I, Nagy Z, Ujj G, Szerafin L, Illes A. Combined prognostic value of absolute lymphocyte/monocyte ratio in peripheral blood and interim PET/CT results in Hodgkin lymphoma. Int J Hematol. 2016;103(1):63-9. doi: 10.1007/s12185-015-1884-z.

19. Belotti A, Doni E, Bolis S, Rossini F, Casaroli I, Pezzatti S, Pogliani EM, Piotelli PE. Peripheral blood lymphocyte/monocyte ratio predicts outcome in follicular lymphoma and in diffuse large B-cell lymphoma patients in the rituximab era. Clin Lymphoma Myeloma Leuk. 2015;15(4):208-13. doi: 10.1016/j.clml.2014.10.001. Epub Oct 23.

20. Lee SF, Luque-Fernandez MA. Prognostic value of lymphocyte-to-monocyte ratio and neutrophil-to-lymphocyte ratio in follicular lymphoma: a retrospective cohort study. BMJ Open. 2017;7(11):e017904. doi: 10.1136/bmjopen-2017-.

21. Boo SH, O JH, Kwon SJ, Yoo IR, Kim SH, Park GS, Choi BO, Jung SE, Cho SG. Predictive Value of Interim and End-of-Therapy 18F-FDG PET/CT in Patients with Follicular Lymphoma. Nucl Med Mol Imaging. 2019;53(4):263-9. doi: 10.1007/s13139-019-00602-0. Epub 2019 Jun 29.

22. Adams HJA, Nievelstein RAJ, Kwee TC. Prognostic value of interim and end-of-treatment FDG-PET in follicular lymphoma: a systematic review. Ann Hematol. 2016;95(1):11-8. doi: 10.1007/s00277-015-2553-2. Epub 2015 Nov 18.

23. Welaya K, Casulo C. Follicular Lymphoma: Redefining Prognosis, Current Treatment Options, and Unmet Needs. Hematol Oncol Clin North Am. 2019;33(4):627-38. doi: 10.1016/j.hoc.2019.03.003. Epub May 18.

24. Zhou Y, Zhao Z, Li J, Zhang B, Sang S, Wu Y, Deng S. Prognostic values of baseline, interim and end-of therapy (18)F-FDG PET/CT in patients with follicular lymphoma. Cancer Manag Res. 2019;11:6871-6885.(doi):10.2147/CMAR.S216445. eCollection 2019.

25. Yasuda H, Tsukune Y, Watanabe N, Sugimoto K, Uchimura A, Tateyama M, Miyashita Y, Ochi Y, Komatsu N. Persistent COVID-19 Pneumonia and Failure to Develop Anti-SARS-CoV-2 Antibodies During Rituximab Maintenance Therapy for Follicular Lymphoma. Clin Lymphoma Myeloma Leuk. 2020;20(11):774-6. doi: 10.1016/j.clml.2020.08.017. Epub Aug 22.

26. Trotman J, Fournier M, Lamy T, Seymour JF, Sonet A, Janikova A, Shpilberg O, Gyan E, Tilly H, Estell J, Forsyth C, Decaudin D, Fabiani B, Gabarre J, Salles B, Van Den Neste E, Canioni D, Garin E, Fulham M, Vander Borght T, Salles G. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol. 2011;29(23):3194-200. doi: 10.1200/JCO.2011.35.0736. Epub 2011 Jul 11.

27. Luminari S, Biasoli I, Versari A, Rattotti S, Bottelli C, Rusconi C, Merli F, Spina M, Ferreri AJ, Zinzani PL, Gallamini A, Franceschetti A, Boccomini C, Franceschetti S, Salvi F, Raimondo FD, Carella AM, Micol Q, Balzarotti M, Musto P, Federico M. The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL). Ann Oncol. 2014;25(2):442-7. doi: 10.1093/annonc/mdt562. Epub 2014 Jan 10.
28. Trotman J, Luminari S, Boussetta S, Versari A, Dupuis J, Tychyj C, Marcheselli L, Berriolo-Riedinger A, Franceschetto A, Julian A, Ricard F, Guerra L, Haioun C, Biasoli I, Tilly H, Federico M, Salles G, Meignan M. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. Lancet Haematol. 2014;1(1):e17-27. doi: 10.1016/S2352-3026(14)70008-0. Epub 2014 Sep 17.

Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.