

Abstract

Introduction: Follicular lymphoma (FL) is an indolent, yet heterogeneous, B-cell lymphoproliferative disorder. Although most FL patients respond well to treatment, few with specific traits have a poor prognosis; the latter are difficult to define.

Patients and methods: We retrospectively analyzed data from 143 FL patients treated at the University of Debrecen since 2009 and investigated prognostic factors that may influence the survival of FL patients.

Results: A maximum standardized uptake value (SUVmax) cut-off of 9.85 at the staging positron emission tomography/computed tomography (PET/CT) (p=0.0001, hazard ratio [HR]: 0.2535, 95% confidence interval [CI]: 0.1118-0.4878) and a lymphocyte/monocyte (Ly/Mo) ratio of 3.41 (p=0.0027, HR: 2.997, 95% CI: 1.463-6.142), drawn at diagnosis, significantly predicted FL patients' progression-free survival (PFS). A staging SUVmax >9.85 with Ly/Mo <3.41 could delineate a high-risk group of FL patients (p<0.0001, HR: 0.0957, 95% CI: 0.03416-0.2685). Similarly, a significant difference was shown with an SUVmax cut-off of 3.15 at the interim PET/CT (p<0.0001, HR: 0.1614, 95% CI: 0.06684-0.3897). A staging SUVmax >9.85 in conjunction with interim SUVmax >3.15 predicted poor prognosis (p<0.0001, HR: 0.1037, 95% CI: 0.03811-0.2824). The PFS difference was translated into overall survival (OS) advantage (p=0.0506, HR: 0.1187, 95% CI: 0.01401-1.005).

Conclusion: Biological prognostic factors, such as the Ly/Mo ratio, may improve the prognostic assessment of staging PET/CT. The survival advantage observed in PFS is translated into OS when determined using a combination of staging and interim SUVmax. We recommend investigating additional biological prognostic factors while highlighting the role of PET/CT in FL.

Background

- Follicular lymphoma (FL) is an indolent, germinal center B-cell–derived lymphoproliferative disease.
- FL is a biologically and clinically heterogeneous disease with wide variation in the outcomes of individual patients.
- Most patients eventually relapse.
- The ability to provide individualized treatment based on the risk assessment of individual FL patients is the subject of ongoing research.
- Unfortunately, such FL patients, who may have a poor prognosis, cannot be distinguished from the rest in advance.
- Hence, it is necessary to precisely predict patient outcomes.

Patients & Methods

- We retrospectively investigated the prognostic factors of FL patients treated between May 2009 and June 2020 at the University of Debrecen, Department of Hematology.
- This retrospective analysis was approved by the Regional and Institutional Research Ethics Committee of the University of Debrecen (DE RKEB/IKEB 5694-2021).
- Factors that may have influenced survival include histology, age, stage, sex, staging-, interim- and restaging maximum standardized uptake value (SUVmax), presence or absence of B symptoms, bone marrow involvement, Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin, LDH, beta-2 microglobulin, absolute lymphocyte (Ly), and monocyte (Mo) count, and lymphocyte/monocyte (Ly/Mo) ratio.
- Patient outcomes were analyzed based on progression-free survival (PFS) and overall survival (OS).
- PFS was calculated from diagnosis to June 2020, relapse or progression of disease, histological transformation, or death, whereas OS was calculated from diagnosis to June 2020 or death.
- Factors that could affect survival were evaluated using a univariate analysis.
- Continuous variables were transformed to discrete either by exceeding normal values or calculating data cut-off values based on the receiver operating characteristic (ROC) curves.
- A multivariable Cox regression model with the Enter method was used to obtain the hazard ratio (HR).
- Survival was estimated using the Kaplan–Meier method.
- Comparison of survival curves was based on the log-rank test.
- Statistical significance was set at p<0.05.

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Patients	143
Female	80
Age (yrs, median, range)	54 (25-85)
Follow up (months, median, range)	54 (3-136)
B symptoms	55
Extranodal involvement	80
Bone marrow involvement	68
Histology	
Grade 1	43
Grade 2	48
Grade 3a	27
Grade 3b	7
FL ND	18
Stage	
I.	15
II.	14
III.	40
IV.	73
ND	1

Staging PET/CT cases	114
Interim PET/CT cases	64
Restaging PET/CT cases	80
First line treatment	
W&W	16
RT	3
R mono	2
R-CVP	16
R-CHOP (CEOP)	65
R-benda	34
G-benda	7

Table 1. Patient characteristics. ND – not defined, W&W – watch and wait, RT – radiotherapy, R – rituximab, CVP - cyclophosphamide, vincristine, prednisolone, CHOP - cyclophosphamide, doxorubicin, vincristine, prednisolone, CEOP – cyclophosphamide, etoposide, vincristine, prednisolone, benda – bendamustin

	Univariate analysis (PFS)			
	Sig.	HR	95,0% CI for HR	
Histology	0,929	6856,187	0,000	4,292E+87
Age >65 yrs	0,058	0,371	0,133	1,035
Gender	0,107	0,620	0,347	1,109
Staging SUVmax >9.85	0,001	3,531	1,650	7,553
Interim SUVmax >3.15	0,0004	6,192	2,266	16,919
Restaging SUVmax >2.68	0,011	3,033	1,295	7,104
Stage	0,233	2,488	0,557	11,119
B-symptoms	0,682	1,142	0,606	2,151
Bone marrow involvement	0,893	0,956	0,495	1,845
ECOG	0,255	2,382	0,534	10,625
Hgb <120 g/L	0,097	1,972	0,885	4,396
LDH >220 U/L	0,014	3,032	1,250	7,355
B2M >2.53 mg/L	0,822	1,099	0,485	2,491
Ly >3.10 G/L	0,230	1,797	0,690	4,682
Mo >0.9 G/L	0,006	5,609	1,636	19,230
Ly/Mo ratio <3.41	0,005	2,963	1,395	6,295
Extranodal involvement	0,923	1,040	0,470	2,302

	Multivariate analysis (Enter method) 1. (PFS)				
	Sig.	HR	95,0% CI for HR		
LDH >220 U/L	0,776	0,840	0,252	2,798	
Ly/Mo ratio <3.41	0,502	1,538	0,438	5,403	
Interim SUVmax >3.15	0,021	5,007	1,277	19,633	
Staging SUVmax >9.85	0,036	5,609	1,124	27,992	

	Multivariate analysis (Enter method) 2. (PFS)				
	Sig.	HR	95,0% CI for HR		
LDH >220 U/L	0,778	1,155	0,423	3,152	
Ly/Mo ratio <3.41	0,035	2,648	1,069	6,558	
Staging SUVmax >9.85	0,008	3,929	1,438	10,735	

Table 2. Univariate and multivariate analysis of prognostic factors that could possibly affect survival of follicular lymphoma patinets'. PFS – progression-free survival, SUVmax – maximum of standardized uptake value, ECOG - Eastern Cooperative Oncology Group, Hgb – hemoglobin, B2M - beta-2 microglobulin, Ly – lymphocyte, Mo – monocyte, LDH – lactate dehydrogenase, Sig. – significance, HR – hazard ratio, CI – confidence interval

References

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Results

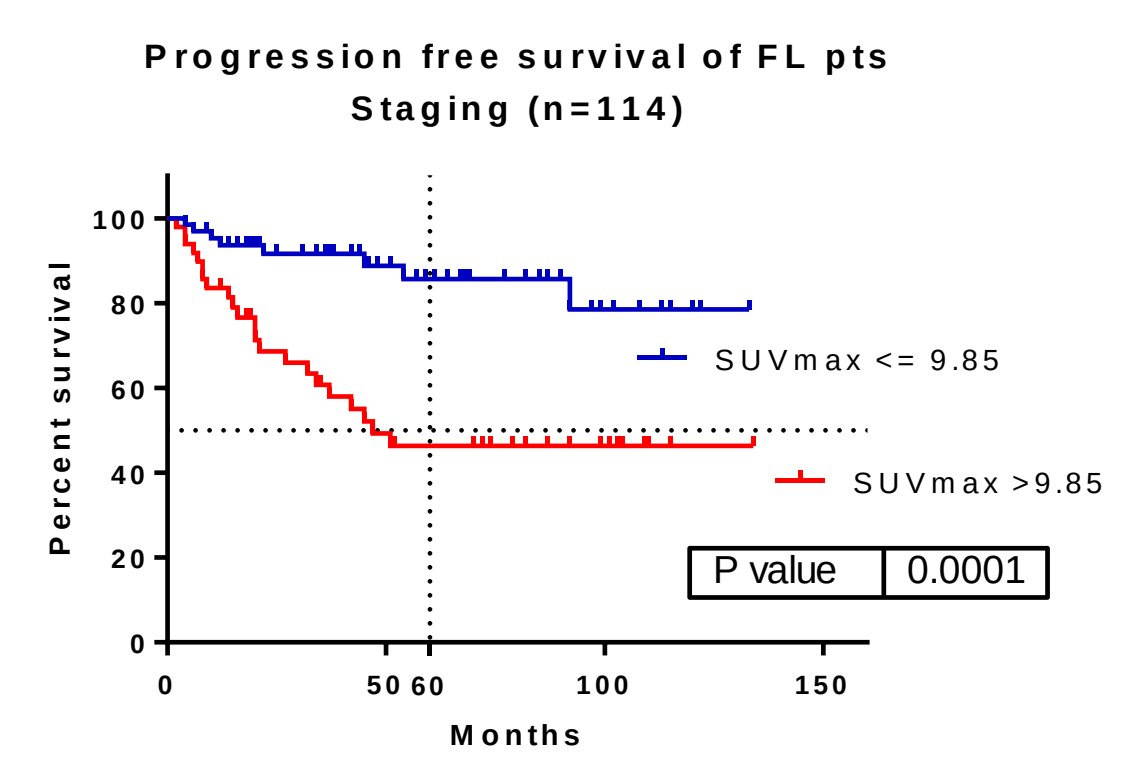


Figure 1. We found a SUVmax cut-off value of 9.85 at the staging PET/CT to significantly separate follicular (FL) patients' progression-free survival (PFS) (p=0.0001, HR: 0.2535, 95%CI: 0.1118-0.4878). Five-year PFS was 85.63 vs. 46.36%. SUVmax – maximum of standardized uptake value

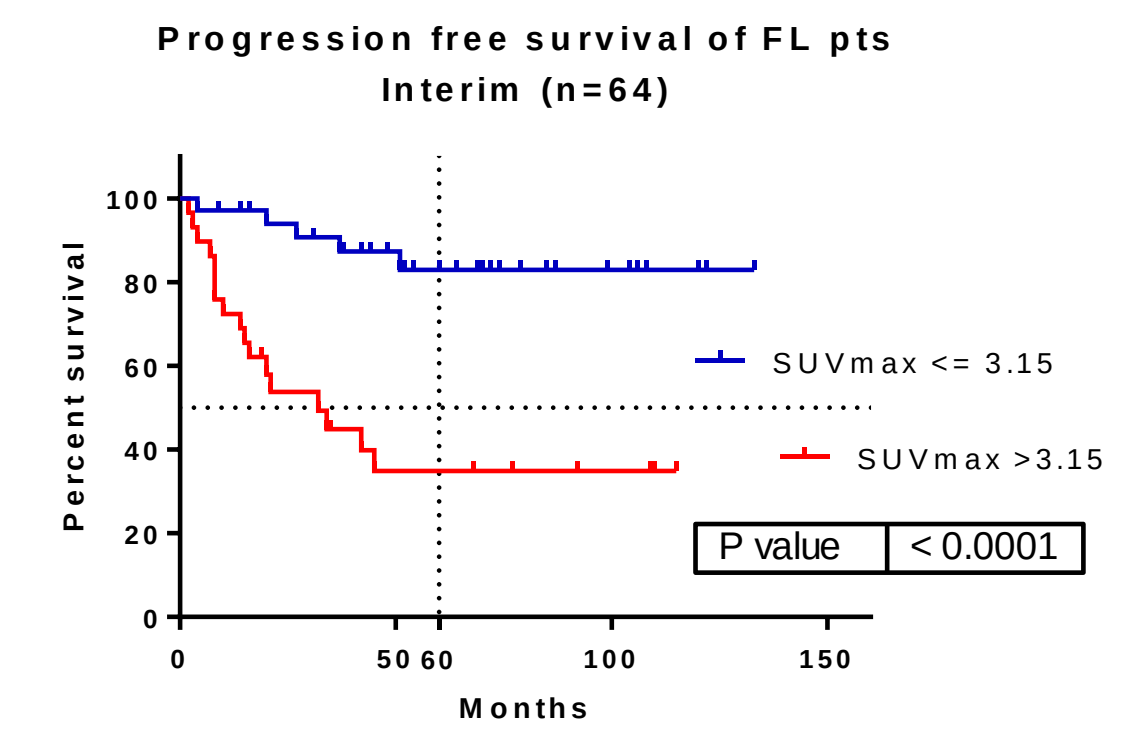


Figure 2. A significant progression-free survival (PFS) difference was shown with a SUVmax cut-off of 3.15 at the interim PET/CT (p<0.0001, HR: 0.1614, 95%CI: 0.06684-0.3897). Five-year PFS was 82.94 vs. 34.86%. SUVmax – maximum of standardized uptake value

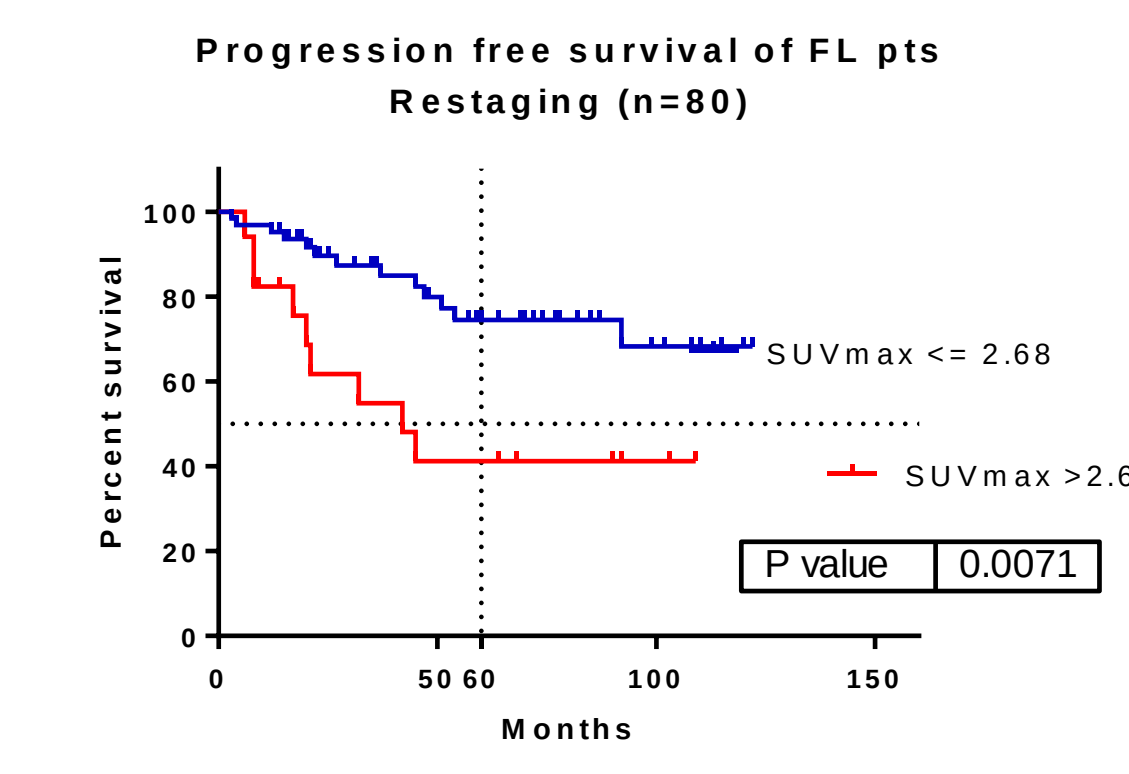


Figure 3. A significant progression-free survival (PFS) difference was shown with a SUVmax cut-off of 2.68 at the restaging PET/CT (p=0.0071, HR: 0.2276, 95%CI: 0.07753-0.6683). Five-year PFS was 74.48 vs. 41.17%. SUVmax – maximum of standardized uptake value

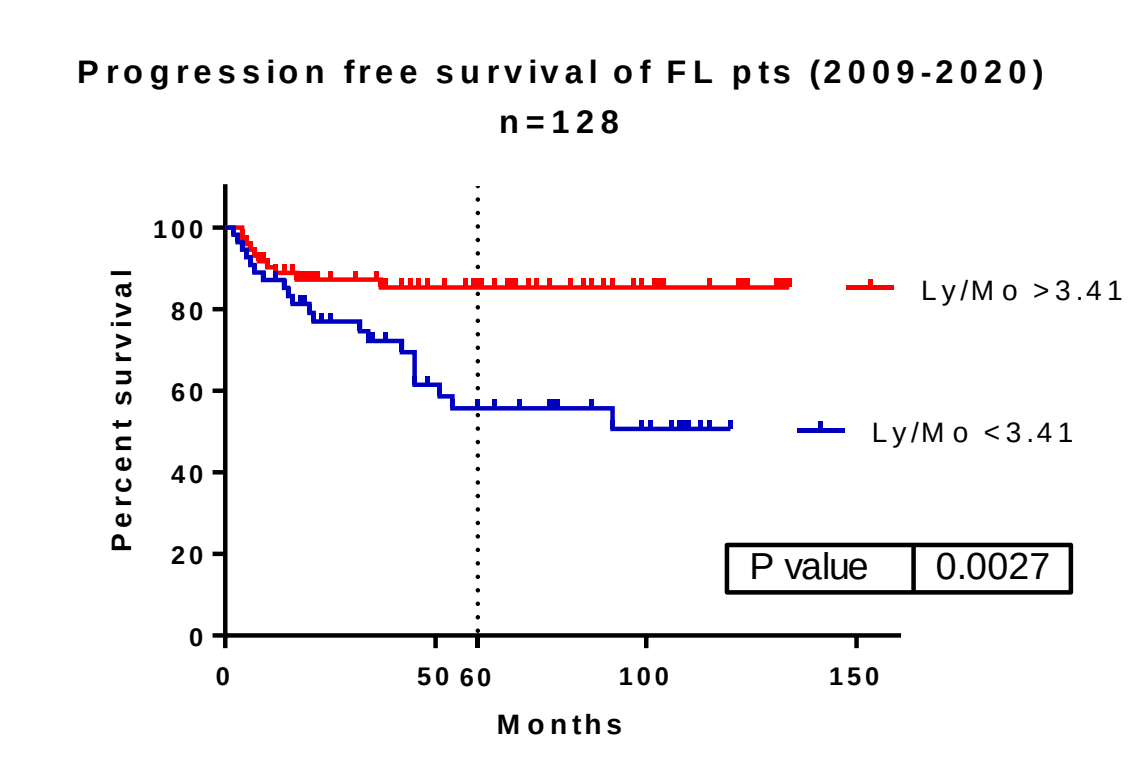


Figure 4. Lymphocyte/ monocyte (Ly/Mo) ratio of 3.41 drawn at diagnosis also significantly predicted PFS (p=0.0027, HR: 2.997, 95% CI: 1.463-6.142). Five-year PFS was 85.30 vs. 55.73%. PFS – progression-free survival, Ly – lymphocyte, Mo – monocyte

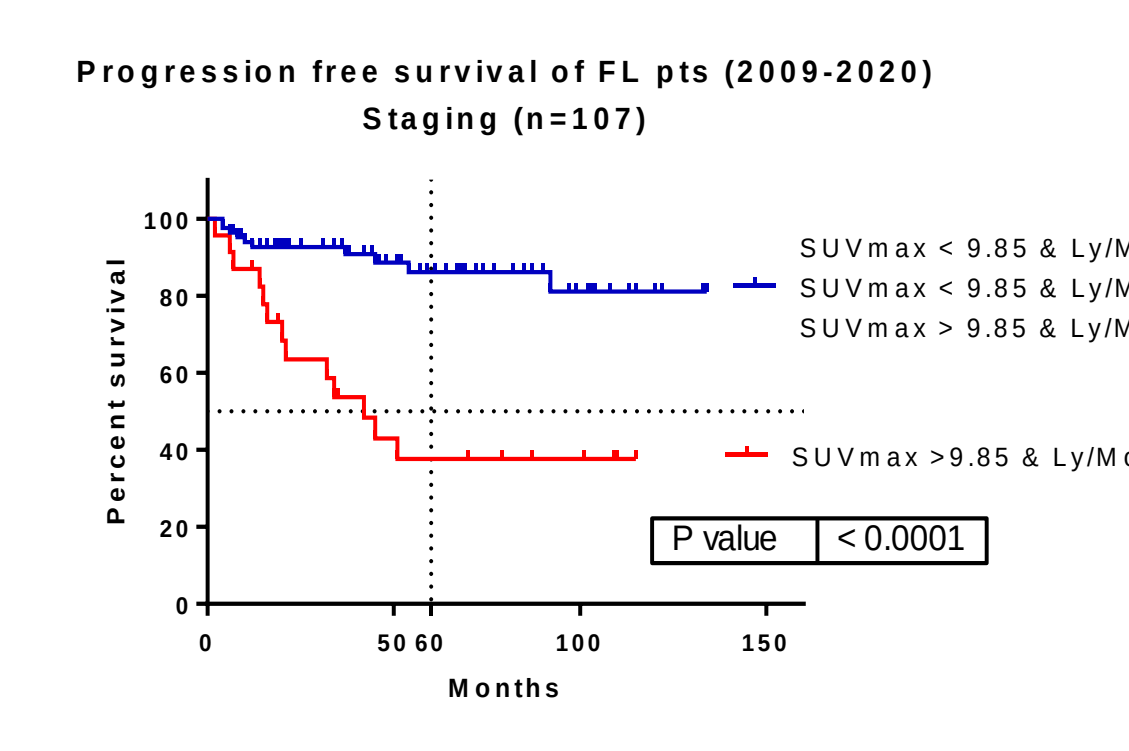


Figure 5. Combining patients with staging SUVmax >9.85 and Ly/Mo < 3.41 a high-risk group of FL patients can be identified (p<0.0001, HR: 0.0957, 95%CI: 0.03416-0.2685). Five-year PFS was 86.16 vs. 37.59%. SUVmax – maximum of standardized uptake value, Ly – lymphocyte, Mo – monocyte

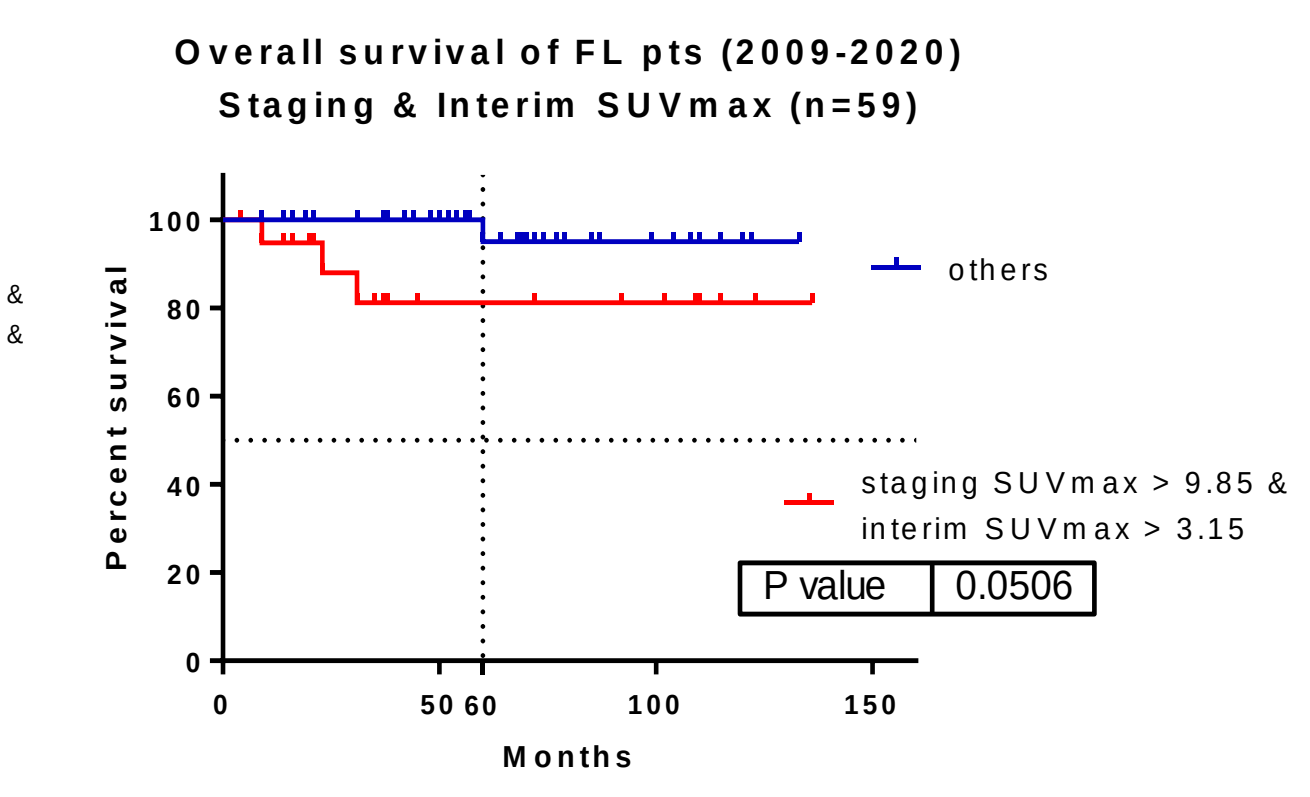
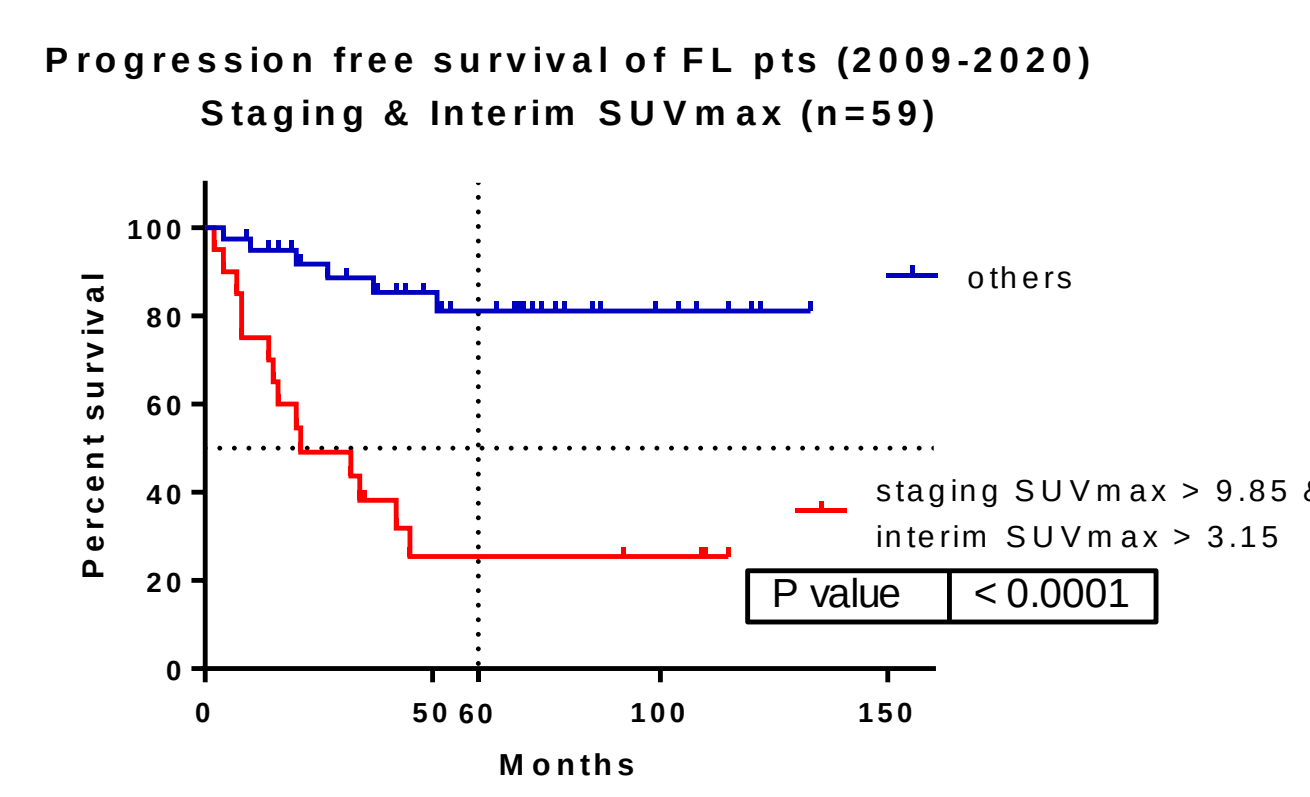


Figure 6. Combining patients with staging SUVmax >9.85 and interim SUVmax >3.15, a high-risk group of FL patients can be identified (p<0.0001, HR: 0.1037, 95%CI: 0.03811-0.2824). Five-year PFS was 81.035 vs. 25.45%. The PFS difference is translated into OS disadvantage (p=0.0506, HR: 0.1187, 95%CI: 0.01401-1.005). Five-year OS was 95.00 vs. 81.20%. SUVmax – maximum of standardized uptake value

Discussion

- By combining staging and interim SUVmax and grouping patients as per the cut-offs, we could identify a difference in the overall survival.
- Our findings show that the combined use of staging and interim SUVmax could have better prognostic value in FL than using only either of the two values.
- We infer that biological prognostic factors, such as the Ly/Mo ratio, are essential because they may improve the prognostic assessment of staging PET/CT.