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Outcomes in grade 3B follicular lymphoma: an international study led by the Australasian Lymphoma Alliance

by Allison Barraclough, James T. England, Diego Villa, Joel Wight, Greg Hapgood, Jason Conn, Nicole Wong Doo, Eric Wenlong Li, Michael Gilbertson, Briony Shaw, Mark J. Bishton, Malik Saeed, Sumita Ratnasingam, Chathuri Abeyakoon, Geoff Chong, Shin Hnin Wai, Matthew Ku, Hui-Peng Lee, Kathryn Fleming, Constantine Tam, Genevieve Douglas, Chan Y. Cheah, Zi Yun Ng, Tukten Rolfe, Anthony K. Mills, Nada Hamad, Helen Cashman, Mary Gleeson, Manjunath Narayana, and Eliza A. Hawkes

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Title: Outcomes in grade 3B follicular lymphoma: an international study led by the Australasian Lymphoma Alliance

Running head: Outcome of grade 3B follicular lymphoma in the rituximab era

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Authors' Contributions

AB designed the research study, contributed and analyzed the data and wrote the paper. EH designed and supervised the research study, analyzed the data and wrote the paper. JE, JW, GH, JC, MG, BS, MB, MS, SR, CA, GC, SHW, MK, HL, KF, CT, GD, CC, ZN, TR, AM, NH, HC, MG, MN and DV contributed data and wrote the paper.

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Data Sharing Statement

The authors will willingly share the original data on requests made by emailing the corresponding author.

Abstract

Grade (G) 3B follicular lymphoma (FL) is a rare FL subtype which exists on a histological continuum between 'low-grade' (Grade 1, 2 and 3A FL) and diffuse large B-cell lymphoma (DLBCL) appearing to share features with each. Clinical characteristics and outcomes are poorly understood due to lack of adequate representation in prospective trials and large-scale analyses. We analyzed 157 G3BFL cases from 18 international centers, and two comparator groups; G3AFL (n=302) and DLBCL (n=548). Composite histology with DLBCL or low-grade FL occurred in approximately half of G3BFL cases. With median 5 years follow-up, G3BFL overall (OS; P<0.001) and progression-free survival (PFS; P<0.001) were superior to DLBCL however G3BFL patients were younger (P<0.001) with better performance status (P<0.001), less extranodal disease (P<0.001) and more frequently normal LDH (P<0.001) at baseline. G3BFL and G3AFL OS and PFS were similar (OS: P=0.83, PFS: P=0.80). After frontline immunochemotherapy, 24% of G3BFL relapsed; DLBCL in 63% and low-grade FL in 19%. 8% of relapses occurred beyond 5 years. In this G3BFL cohort, the R-IPI successfully delineated risk groups, but FLIPI did not. We conclude that immunochemotherapy-treated G3BFL has similar survival outcomes to G3AFL, yet a favourable baseline profile and distinctly superior prognosis compared to DLBCL.

Introduction

Follicular lymphoma (FL) is the most frequent indolent non-Hodgkin lymphoma (NHL), constituting 20-30% of all cases.[1] World Health Organisation (WHO) morphological grading is according to relative proportion of centrocytes to centroblasts.[2] WHO grade 3B follicular lymphoma (G3BFL), the highest grade, comprises only 5-10% of cases [1 3-6] and is differentiated from its lower grade counterpart, grade 3A FL (G3AFL), by the presence of follicles exclusively comprised of centroblasts.[7] While the 2022 revision of the International Consensus Classification of Mature Lymphoid Neoplasms has retained this grading strategy,[8] the recent 5th edition of the WHO diagnostic criteria has revised the FL nomenclature, with G1-3FL now being referred to as classic FL and G3BFL as follicular large cell lymphoma respectively.[9]

Low-grade FL (Grade 1, 2 and 3AFL) typically follows a relapsing-remitting disease course potentially spanning decades, whereas G3BFL is thought to follow a more aggressive clinical course. Published data, however, are conflicting with some G3BFL reports describing an indolent, incurable natural history while others describe rapid initial progression followed by long remissions and potential cure from combination chemotherapy, more akin to diffuse large B-cell lymphoma (DLBCL).[3,4,6,10-15]

Despite histological similarities between G1-G3AFL and G3BFL, treatment guidelines largely recommend rituximab and anthracycline-containing regimens for G3BFL,[16] analogous to DLBCL clinical management. In contrast, low-grade FL management predominantly utilises therapy to control symptomatic disease and achieve durable remission as opposed to cure.[17,18] While historical variation exists for G3AFL therapeutic paradigms,[19,20] G3AFL is currently considered an indolent lymphoma and regularly included in modern-era low-grade FL trials.[17,21,22] Yet, exclusion of G3BFL from both DLBCL and low-grade FL clinical trials and the small heterogeneous cohorts in published retrospective series have limited our understanding of this high-grade FL subgroup and the optimal treatment approach.

Here we describe outcomes of the first large international G3BFL study from the rituximab era. We utilise contemporaneous comparator G3AFL and DLBCL cohorts, to establish prognostic information, survival outcomes and relapse patterns of this rare subtype.

Methods

We developed a database of consecutively treated adult G3BFL patients diagnosed between 2002-2019 from 18 expert lymphoma centers in Australia, UK and Canada. Composite Grade 3A/G3BFL and G3BFL/DLBCL were included in the G3B group. Treatment consisted of rituximab/obinutuzumab, cyclophosphamide, doxorubicin, vincristine and prednisolone(R/O-CHOP)-like chemotherapy with or without radiotherapy (RT). Those receiving RT alone (n=2) or alternate chemotherapy regimens (n=6) were excluded. In this study, FL grading was according to the 4th edition WHO criteria.[7]

Consecutive G3AFL and DLBCL cases from participating institutions were collected for comparison due to the close histological relationships and to establish clinical similarities and differences between these and G3BFL. The G3AFL comparator cases were collected consecutively in the same time frame and by the same contributing sites as the G3BFL group. Treatment was with R-CHOP-like chemotherapy with or without RT or bendamustine-rituximab (BR). The DLBCL cohort were treated with R-CHOP, with or without RT, from 2008-2018 (inclusive) and were identified from 3 of the Australian sites.

The majority of participating sites follow the standard international recommendation of 5 years' follow up in aggressive lymphoma, after which time patients were discharged back to their primary care physician and at which point no further outcome data could be extracted from external sources.

Retrospective data including baseline characteristics, treatment details and outcomes were obtained from registries and tertiary institution medical records. Cases were sourced from centers with established expert lymphoma multidisciplinary meeting histopathology review, as central histological review of all archived cases from the large number of international participating sites was not feasible. Additionally, in order to ensure homogeneity of diagnosis and grading between contributing countries, we analysed PFS according to regions (Australia versus, Canada versus UK) for G3AFL and G3BFL respectively, and demonstrated no statistical difference between regions (G3AFL P=0.78, G3BFL P=0.58). Furthermore, the proportions of G3AFL and G3BFL in our series, are similar to those reported elsewhere.[4,6,15]

Overall survival (OS) was defined as the time from the date of diagnosis until death from any cause, and progression free survival (PFS), as time from diagnosis until relapse/progression (to any B-cell lymphoma subtype) or death from any cause; both calculated according to the Kaplan-Meier method with patients censored at last known follow up if no date of death or progression was recorded.[23] Differences in patient/disease characteristics among groups (G3AFL, G3BFL and DLBCL respectively) were analyzed using Fisher's exact test for discrete variables and the Kruskal-Wallis H test for continuous variables. Differences in OS/PFS were compared using log-rank tests, and associations between prognostic factors, histological subgroup and outcomes were analyzed using Cox proportional hazards models. Variables with P <0.1 on univariable analysis were included in the multivariable analysis, with two tailed P ≤0.05 considered significant. This study was in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 and is approved by institutional review boards at all participating institutions.

Results

A total of 157 G3BFL cases were eligible including 85 pure G3BFL, 24 composite G3A/G3BFL, and 48 composite G3B/DLBCL; collectively the "G3BFL" group. The comparator groups consisted of 302 G3AFL and 548 DLBCL consecutive cases. Baseline clinical and tumour characteristics, treatment and relapse data are summarised in **Table 1**.

For G3BFL, all patients received R or O-CHOP-like chemotherapy with 17% receiving consolidative RT. Fifty-nine patients (37%) received maintenance rituximab or obinutuzumab for a median of 8 cycles (range 1-24). G3AFL patients received R- or O-CHOP-like chemotherapy with or without RT in 74% and BR in 26%; with 68% receiving maintenance therapy for a median of 8 cycles (range 1-24).

Median follow-up of the entire cohort was 5 years (range 0.03-16.11 years). Five year survival of pure G3BFL, composite G3A/3BFL and G3BFL/DLBCL were not significantly different (PFS: G3BFL 60% (95% CI 46-71%), G3A/3BFL 79% (95% CI 54-92%), G3B/DLBCL 70% (95% CI 51-83%) *P*=0.51; OS: G3BFL 80% (95% CI 67-88%), G3A/3BFL 86% (95% CI 54-96%), G3B/DLBCL 87% (95% CI 71-95%) *P*=0.37) and therefore this group was analyzed together. The G3BFL group 5-year PFS was 66% (95%CI: 57-75%) and OS was 84% (95%CI: 76-89%). While outcomes were similar between G3AFL and the G3BFL group (OS: 1.04 (95%CI 0.67-1.65) *P*=0.84; PFS: HR 1.04 (95%CI 0.75-1.46) *P*=0.81), the G3BFL group had superior PFS and OS to DLBCL (OS: HR 2.19 (95%CI 1.45-3.29) *P*=<0.001; PFS: HR 1.73 (95%CI 1.27-2.63) *P*=0.001). No plateau was observed on the G3BFL PFS curve **(Figure 1A and B).** No difference in survival was demonstrated between R-CHOP treated G3AFL and G3BFL (OS: HR 0.98 (95%CI 0.60-1.60) *P*=0.93; PFS HR 0.98 (95%CI 0.68-1.40) *P*=0.89) **(Figure 2A and B)**.

On univariate analysis of the entire cohort, candidate factors that were statistically significant for PFS and OS were age >60 years, male gender, elevated baseline LDH, stage III/IV, ECOG 3-4 and extranodal involvement. Stage III/IV disease and extranodal involvement did not retain significance

on multivariable analysis. DLBCL was associated with inferior PFS and OS on both univariate and multivariate analysis, whereas G3AFL and G3BFL did not display a difference in outcome. The DLBCL cohort PFS and OS HR were 1.27 (95%CI 1.00-1.62; *P*=0.05) and 1.53 (95%CI 1.12-2.08; *P*=0.007) respectively, whereas G3AFL PFS and OS HR were 0.97 (95%CI 0.69-1.35; *P*=0.84), and 0.96 (96% CI 0.61-1.51; *P*=0.86) respectively. The G3BFL PFS HR was 0.81 (95%CI 0.54-1.2; *P*=0.30) and OS HR 0.86 (95%CI 0.51-1.47; *P*=0.59). Also see **Table 2**.

The proportion of relapses and those progressing within 24 months of diagnosis (POD24)[24] was similar between G3AFL and the G3BFL group with total relapse proportions and POD24 as follows: G3AFL 29% and 18%, G3BFL 25% and 19%. The median time to relapse (TTR) was 19 months (range 1-155) for G3AFL and 13 months (range 4-138) for G3BFL. In those who relapsed, no difference in outcomes was seen according to baseline histological grade: PFS HR: 1.04 (95%CI 0.71-1.54) *P*=0.81; OS: HR 1.10 (95%CI 0.62-1.95) *P*=0.75. At 2 years, G3BFL patients experiencing POD24, had an inferior OS compared with G3AFL (2-year OS G3AFL 66% (95%CI 51-78%), G3BFL 34% (95 CI 14-57%); *P*=0.05).

Of the 39 relapses in the G3BFL group, 27 had biopsy confirmation. Histology at relapse was G1/2FL in 2 (7%), G3AFL in 3 (11%), G3BFL in 5 (18%) and DLBCL in 17 (63%). Of those that relapsed/transformed to DLBCL, diagnostic histology was G3A/BFL in 2 patients (12%), G3BFL in 10 patients (59%) and G3BFL/DLBCL in 5 patients (29%). The median TTR with FL histology was 28 months (range 5-138) and with DLBCL 18 months (range 4-59). Patterns of relapse according to histological subtype are presented in **Figure 3**. Three of 39 relapses in G3BFL occurred beyond 5 years; at 6, 7.5 and 11.5 years and histology was G1-2FL, G3AFL and G3BFL respectively.

In G3BFL, 27 deaths were reported. Of these, 15 were attributable to lymphoma. Six deaths occurred beyond 5 years from the initial G3BFL diagnosis, all due to non-lymphomatous causes. In the G3AFL

cohort, 62 deaths were recorded, in which 38 were due to lymphoma. Nineteen deaths occurred more than 5 years after initial lymphoma diagnosis, of which 6 were caused by lymphoma. In the DLBCL cohort, 179 deaths occurred. Lymphoma was the cause of death in 118 cases with 19 deaths occurring beyond 5 years, 9 of which were caused by lymphoma.

Univariable analysis of candidate prognostic factors in G3BFL for PFS and OS is presented in **Table 3.** CD10 immunohistochemical (IHC) negativity and Ann Arbor stage III/IV disease were associated with inferior PFS; while elevated LDH, Eastern Cooperative Oncology Group (ECOG) performance status 3-4 and age >60 years were associated with inferior OS. Factors that retained significance on multivariable analysis were ECOG 3-4 for PFS and OS and stage III/IV disease for PFS. Of note, our series did not show an OS or PFS advantage with the addition of MR or O to front-line immunochemotherapy in G3BFL (OS HR: 0.32 (95%CI 0.07-1.59) *P*=0.17; PFS HR: 0.91 (95%CI 0.38-2.18) *P*=0.84), with the caveat of non-uniform administration and treatment cycle length **(Table 3)**.

The prognostic utility of the Follicular Lymphoma International Prognostic Index (FLIPI)[25] and the revised International Prognostic Index (R-IPI)[26] for G3BFL were assessed. The FLIPI showed poor discrimination of risk groups with low, intermediate and high risk 5-year OS of 100%, 80% and 81% respectively (*P*=0.19). The R-IPI showed a statistically significant difference between risk groups with low, intermediate and high risk 5-year OS of 100%, 85% and 64% respectively (*P*=<0.001) **(Figure 4A and B)**.

Discussion

This international analysis of G3BFL, uniformly treated R-CHOP (like) chemotherapy, is the largest and most comprehensive of its kind. By comparing with contemporaneous G3AFL and DLBCL cohorts, of which the vast majority were also treated with R-CHOP (like) therapy, we found that G3BFL has a superior prognosis to DLBCL. Moreover, G3AFL and G3BFL had very similar progression-

free and overall survival outcomes. These key findings indicate that G3BFL behaves similarly to G3AFL, but distinct from DLBCL.

The historically described aggressive behaviour of G3BFL is based on small (n<25), retrospective cohorts predominantly treated in the pre-rituximab era.[5,11,13,14] However, in our dataset, both PFS and OS for G3BFL were markedly superior to DLBCL. Interestingly, patients with composite G3BFL and DLBCL histology experienced similar survival outcomes to patients with pure G3BFL, rather than DLBCL. This was not due to treatment, as both cohorts uniformly received R/O-CHOP. This contrasts with the series from Yuen *et al*[27] showing outcomes of 17 G3BFL versus DLBCL to be similar (OS *P*=0.42, EFS *P*=1.0). Our results may in part be due to the more favourable baseline clinical prognostic profile of G3BFL compared to DLBCL. G3BFL patients were found to be younger with a better performance status, less frequent extranodal involvement and/or baseline elevated LDH. However, our multivariable analysis, accounting for these differences, demonstrated only DLBCL to have inferior outcomes.

In addition to the similar survival outcomes of G3AFL and G3BFL, the POD24 rate and continuous pattern of relapse were also similar for the follicular histologies. This was despite the use of bendamustine for a quarter of G3AFL patients, compared to nearly all G3BFL patients receiving R/O-CHOP. The proportion of relapses with DLBCL histology was similar for G3AFL and G3BFL. Baseline clinical characteristics were well balanced, as were FLIPI and R-IPI profiles. While outcomes of G3BFL and G3AFL were equivalent with R-CHOP, it is not known if bendamustine-based therapy for G3BFL would have yielded equivalent outcomes. Unlike previous small series[4,15], our data suggest that G3BFL may not consistently be curable as evidenced by the continuous pattern of relapse.

Previous studies comparing G3AFL and G3BFL report conflicting results. In a study of 345 FL patients, G3BFL (n=23) had a higher mortality compared with G1-3AFL, independent of clinical factors

(P<0.01).[4] However, only 9% of G3BFL patients received frontline rituximab; although anthracycline was used in 70% compared with 30% of G1-2FL and 43% of G3AFL. Another small study (17 G3BFL) displayed inferior outcomes compared to G3AFL using rituximab and anthracycline therapy (P=0.043).[27] In contrast, Shustik *et al*,[6] found equivalent outcomes in G3AFL and G3BFL (n=22); again, not all received rituximab. Interpretation of these three studies is hampered by small G3BFL numbers and non-uniform rituximab use.

In our study the proportion of G3BFL patients expressing CD10 and BCL2 by IHC was significantly lower compared to G3AFL. This is corroborated by prior studies, demonstrating pure G3BFL and composite G3B/DLBCL can lack CD10 and BCL2 contrasting with that of G1-3AFL, which typically has uniform CD10, BCL2 and BCL6 expression. [28,29] Additionally, our data and others have shown the median Ki-67 proliferation index increases proportionally with FL grade[28] but is lower than that seen with DLBCL. To further characterise these laboratory-based differences, two recent studies utilised gene expression profiling techniques with differing results. Horn *et al* failed to observe a significant difference in the gene expression patterns between G3A and G3B FL, while in a supervised analysis approach, Piccaluga *et al* demonstrated G3BFL formed a single cluster, distinct from FL G1/2 and G3AFL. Low case numbers (6 and 4 respectively) and differing gene sets likely contributed to this discrepancy. Further molecular studies are needed to examine the biological differences between these FL subgroups.

The original FLIPI[25] and R-IPI[26] score studies did not include G3BFL in their primary analyses, hence their utility is not clear in this group. For the first time, we have shown that the R-IPI retains prognostic significance with G3BFL, yet the FLIPI score does not. Given the excellent delineation between risk groups using the R-IPI, our results support the R-IPI as an accurate baseline prognostication tool for G3BFL.

Our study shows a higher rate of R-IPI high risk patients in the DLBCL cohort compared to the G3AFL and G3BFL cohorts. Additionally, compared to DLBCL, G3BFL patients presented more commonly with LDH within the normal range, a lower median ki67 and less frequently with extranodal site involvement, reflecting a more favourable disease "signature". These factors likely contribute to the favorable outcomes of G3A and G3BFL described in our study compared to DLBCL.

There are a number of limitations to this study. We acknowledge the inherent limitations of retrospective data collection and analyses. The practice of discharging aggressive lymphoma patients after 5 years' follow-up and the inability to collect ongoing outcome data after this time-point may contribute to survivorship bias. While it is recognised that relapses after 5 years are rare for DLBCL, this may not be the case with G3BFL so longer-term conclusions should be made with caution. Also, central pathology review of the entire cohort by a single pathologist was not possible however we limited study participation to institutions with local lymphoma pathological expertise and routine lymphoma multidisciplinary meeting case reviews. Even with the harmonisation of criteria for FL grading we acknowledge concordance and reproducibility challenges in grading of G3FL.[1,29] Nonetheless, with global central review not feasible in routine care, our international collaboration, with designated expert centers presents a real-world large international cohort. Further, whilst relapse proportions were reported, follow-up was not uniform between patients and not all cases had biopsy information available, as such these results should be interpreted with caution. Additionally, limited IHC and fluorescent in situ hybridization (FISH) diagnostic data was available/provided and this precluded a detailed analysis in this regard. We also acknowledge that the DLBCL cases were collected from 2008 onwards from a limited number of representative centers, while the indolent cases were from 2002 onwards. This decision was due to feasibility of collecting thousands of DLBCL cases as DLBCL is far more common, and due to the stable outcomes of DLBCL seen in both trials and retrospective cohorts across the rituximab era. The similar outcomes from our cohort compared to other large DLBCL real-world studies are reassuring.[26,30,31]

On the basis of this analysis, G3BFL should be considered prognostically similar to G3AFL, and distinct from DLBCL. Because our G3BFL cohort was uniformly treated with R/O-CHOP, we cannot currently recommend alternative regimens used for lower grade FL. Nevertheless, we suggest that upfront clinical trials for follicular lymphoma that incorporate anti-CD20 monoclonal antibody and CHOP, include both G3AFL and G3BFL. Due to the marked difference in outcomes compared to DLBCL, it seems appropriate to exclude G3BFL from front-line DLBCL clinical trials. Further research to improve the molecular classification of G3BFL may assist in developing specific treatments for this rare subgroup.

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Table 1. Clinical characteristics, treatment and outcome summary

Characteristic	G3A (n=302)	G3B group (n=157)	DLBCL (n=548)	*P value*
Age (years)				
median, range	62 (22-86)	63 (18-86)	68 (20-92)	**<0.001**
>60 years (%)	169 (56)	85 (54)	394 (72)	**<0.001**
Sex (%)				
Male	150 (50)	87 (55)	317 (58)	0.07
Stage at diagnosis (%)				
I/II	51 (17)	48 (31)	176 (32)	**<0.001**
III/IV	247 (83)	109 (69)	371 (68)	
Performance status (%)				
ECOG 1-2	255 (94)	147 (95)	448 (87)	**<0.001**
ECOG 3-4	15 (6)	7 (5)	65 (13)	
LDH > ULN (%)	70 (28)	59 (38)	306 (62)	**<0.001**
ki67, median (range)	50 (5-99)	72 (30-100)	85 (5-100)	**<0.001**
Extranodal site (%)	157 (52)	76 (49)	366 (67)	**<0.001**
Bulk >7cm (%): follicular lymphoma	77 (33)	38 (27)	*	0.25
CD10 IHC positive (%)	255 (91)	116 (78)	*	**<0.001**
BCL2 IHC positive (%)	250 (90)	112 (76)	*	**0.001**
FLIPI (points)				
Low (0-1)	11 (5)	25 (17)	*	**0.002**

Intermediate (2)	59 (29)	41 (27)	*	
High (3-4)	139 (66)	83 (56)	*	
R-IPI (points)				
Low (0)	8 (5)	24 (16)	35 (7)	**<0.001**
Intermediate (1-2)	138 (71)	89 (59)	215 (42)	
High (3-5)	47 (24)	38 (25)	262 (51)	
Treatment				
R/O-CHOP (like) +/- Radiotherapy	223 (74)	157 (100)	548 (100)	**<0.001**
BR	79 (26)	0 (0)	0 (0)	
Anthracyclines	217 (72)	151 (96)	548 (100)	**<0.001**
No Anthracyclines	85 (28)	6 (4)	0 (0)	
Maintenance therapy	205 (68)	59 (37)	*	**<0.001**
Relapse (%)	87 (29)	39 (25)	*	0.21
POD event in first 24 months (%)	48 (18)	22 (19)	*	0.89
Histology at Relapse				
Grade 1/2	9 (17)	2 (7)	*	**0.02**
Grade 3A	14 (26)	3 (11)	*	
Grade 3B	1 (2)	5 (18)	*	
DLBCL	30 (56)	17 (63)	*	

* Not available

Table 1. Clinical characteristics, treatment and outcome summary

G grade, DLBCL diffuse large B cell lymphoma, ECOG Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, ULN upper limit normal, IHC immunohistochemistry, FLIPI Follicular Lymphoma International Prognostic Index, R-IPI revised International Prognostic Index, R/O-CHOP rituximab obinutuzumab cyclophosphamide doxorubicin vincristine prednisolone, POD24 Progression of disease within 2 years.

Table 2. Univariable and multivariable analysis of entire cohort

Candidate Factor	Univariable analysis				Multivariable analysis			
	PFS		OS		PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >60 years	3.14 (2.28-4.31)	**<0.001**	3.14 (2.28-4.31)	**<0.001**	1.38 (1.09-1.76)	**0.008**	3.02 (2.11-4.32)	**<0.001**
Male	1.33 (1.04-1.70)	**0.02**	1.33 (1.04-0.17)	**0.02**	1.40 (1.13-1.74)	**0.002**	1.46 (1.12-1.91)	**0.005**
Elevated serum LDH	2.54 (1.95-3.32)	**<0.001**	2.54 (1.95-3.32)	**<0.001**	1.93 (1.53-2.44)	**<0.001**	2.01 (1.51-2.68)	**<0.001**
Stage (III/IV versus I/II)	1.55 (1.16-2.07)	**0.003**	1.55 (1.16-2.07)	**0.003**	1.45 (1.10-1.92)	**0.009**	1.20 (0.87-1.66)	0.27
Extranodal site(s)	1.75 (1.42-2.15)	**<0.001**	1.40 (1.09-1.80)	**0.008**	1.43 (1.13-1.81)	**0.003**	1.10 (0.83-1.46)	0.68
ECOG (3-4 versus 0-2)	3.62 (2.61-5.02)	**<0.001**	3.62 (2.61-5.02)	**<0.001**	2.10 (1.54-2.86)	**<0.001**	2.36 (1.67-3.32)	**<0.001**
Grade 3A FL	0.97 (0.69-1.35)	0.84	0.96 (0.61-1.51)	0.86				
Grade 3B FL	0.81 (0.54-1.21)	0.30	0.86 (0.51-1.47)	0.59				
DLBCL	1.73 (1.41-2.13)	**<0.001**	2.26 (1.74-2.93)	**<0.001**	1.27 (1.00-1.62)	**0.05**	1.53 (1.12-2.08)	**0.007**

Table 2. Univariable and multivariable analysis of entire cohort

PFS progression free survival, OS overall survival, HR hazards ratio, CI confidence interval, LDH lactate dehydrogenase, ECOG Eastern Cooperative Oncology Group, FL follicular lymphoma, DLBCL diffuse large B cell lymphoma.

Table 3. G3B FL univariable and multivariable analysis

Candidate Factor	Univariable analysis				Multivariable analysis			
	PFS		OS		PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >60 years	1.00 (0.57-1.74)	1.00	2.14 (0.96-4.79)	**0.05**	0.96 (0.42-2.19)	0.92	1.90 (0.53-6.87)	0.33
Male	0.76 (0.43-1.32)	0.33	0.96 (0.45-2.04)	0.91				
Elevated serum LDH	2.43 (1.39-4.26)	**0.002**	2.00 (0.94-4.26)	**0.05**	1.68 (0.69-4.09)	0.25	1.98 (0.57-6.94)	0.28
Stage (III/IV versus I/II)	2.76 (1.34-5.72)	**0.006**	1.90 (0.77-4.73)	0.17	3.71 (1.08-12.78)	**0.04**	3.67 (0.45-29.59)	0.22
Extranodal site(s)	1.20 (0.69-2.09)	0.53	0.65 (0.30-1.42)	0.28				
ECOG (3-4 versus 0-2)	7.11 (2.96-17.08)	**<0.001**	18.25 (6.92-48.08)	**<0.001**	3.92 (0.94-16.28)	**0.05**	6.45 (1.34-31.08)	**0.02**
Bulk	0.13 (0.62-2.11)	0.68	1.13 (0.49-2.61)	0.77				
CD10 IHC	0.50 (0.26-0.93)	**0.02**	0.49 (0.21-1.14)	0.10	0.63 (0.25-1.57)	0.32	0.65 (0.19-2.28)	0.50
BCL2 IHC	1.78 (0.83-3.82)	0.14	1.06 (0.44-2.66)	0.90				
Maintenance Rituximab/Obinutuzumab	0.69 (0.36-1.28)	0.23	0.40 (0.15-1.07)	0.07	0.91 (0.38-2.18)	0.84	0.32 (0.07-1.59)	0.17

Table 3. G3B FL univariable and multivariable analysis

PFS progression free survival, OS overall survival, HR hazards ratio, CI confidence interval, LDH lactate dehydrogenase, ECOG Eastern Cooperative Oncology Group, IHC immunohistochemistry.

Figure Legend

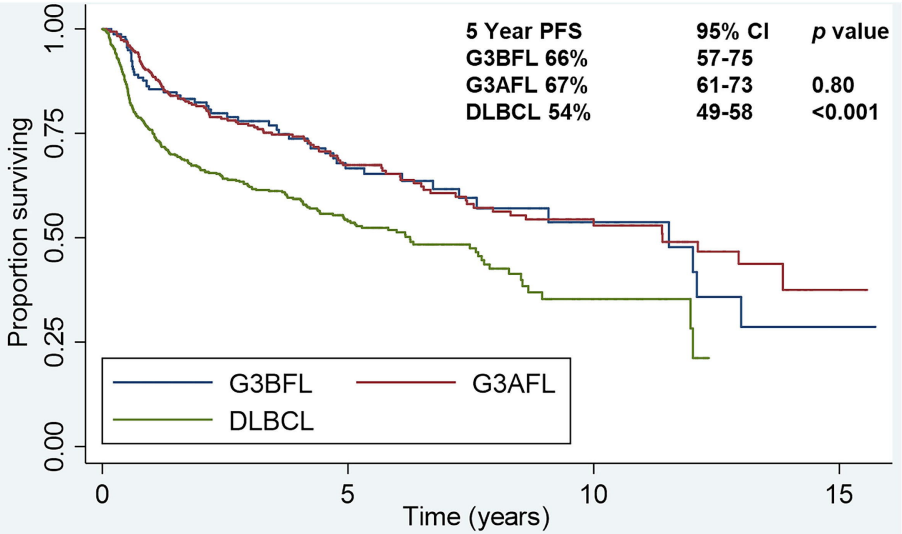
Figure 1. Survival outcomes according to histology.
Figure 1A. Progression free survival according to histology.
Figure 1B. Overall survival according to histology.
G grade, FL follicular lymphoma, DLBCL diffuse large B cell lymphoma, CI confidence interval, PFS progression free survival, OS overall survival.

Figure 2. Survival outcomes with RCHOP by histology.
Figure 2A. Progression free survival with RCHOP by histology.
Figure 2B. Overall survival with RCHOP by histology.
RCHOP rituximab cyclophosphamide doxorubicin vincristine prednisolone, G grade, FL follicular lymphoma.

Figure 3. G3BFL histological grade at relapse.
G grade, FL follicular lymphoma, DLBCL diffuse large B cell lymphoma.

Figure 4. G3BFL survival according to prognostic risk scores.
Figure 4A. G3BFL overall survival according to FLIPI risk score.
Figure 4B. G3BFL overall survival according to R-IPI.
G grade, FL follicular lymphoma, FLIPI Follicular Lymphoma International Prognostic Index, R-IPI revised International Prognostic Index.

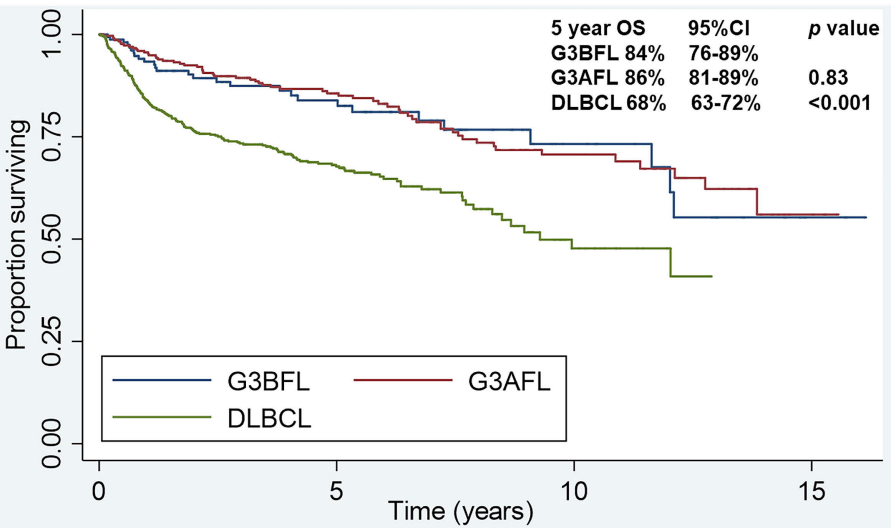
Figure 1A. Progression free survival according to histology.



Number at risk

G3BFL	159	56	13	1
G3AFL	302	117	37	2
DLBCL	548	143	15	0

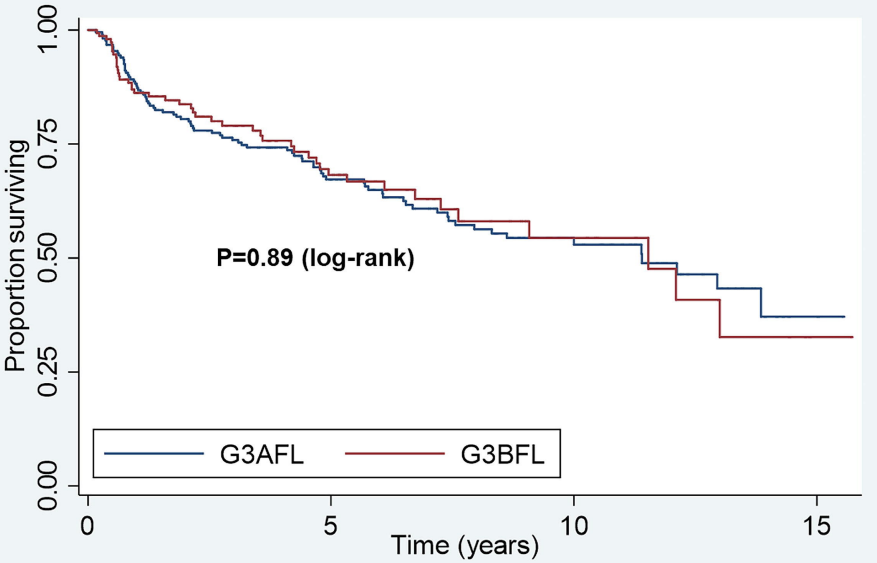
Figure 1B. Overall survival according to histology.



Number at risk

G3BFL	159	64	17	2
G3AFL	302	150	50	4
DLBCL	548	193	21	0

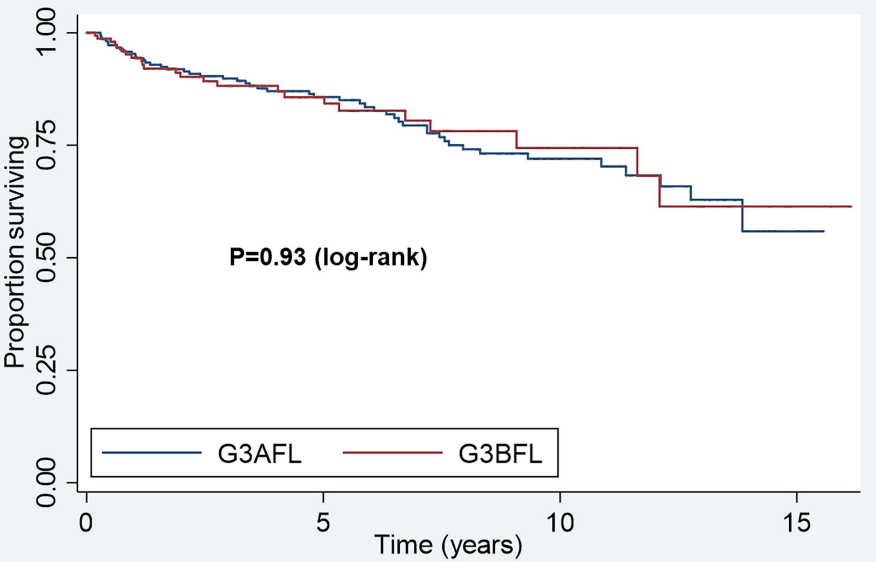
Figure 2A. Progression free survival with RCHOP by histology.



Number at risk

G3A	217	98	36	2
G3B	151	54	12	1

Figure 2B. Overall survival with RCHOP by histology.



Number at risk

G3A	217	125	48	3
G3B	151	62	16	2

Figure 3. G3BFL histological grade at relapse.

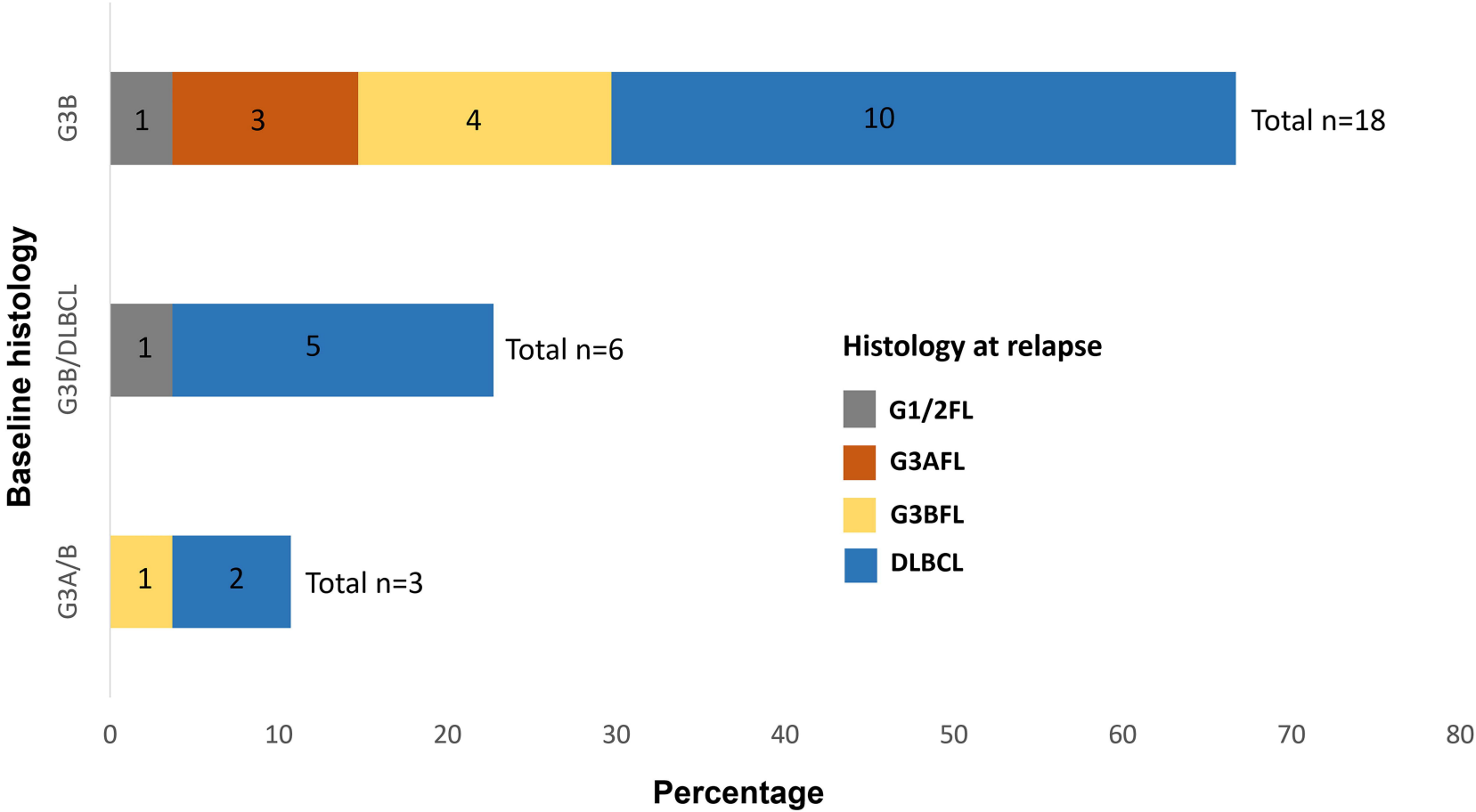
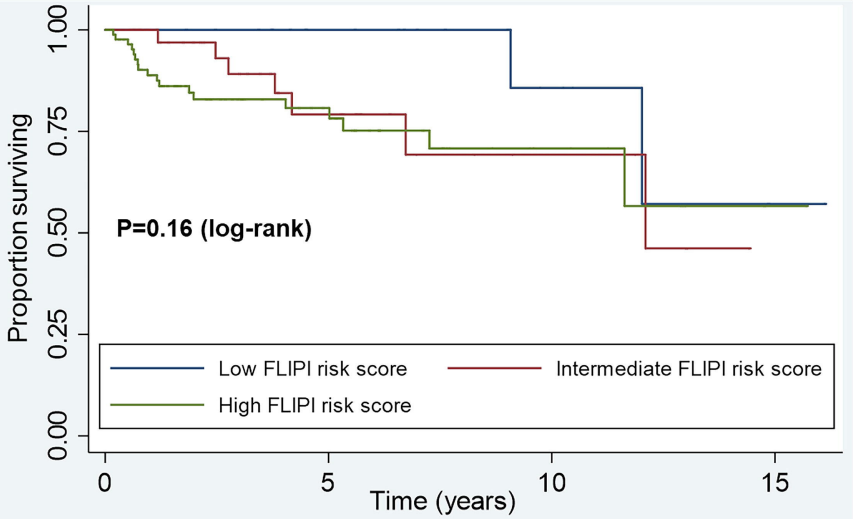
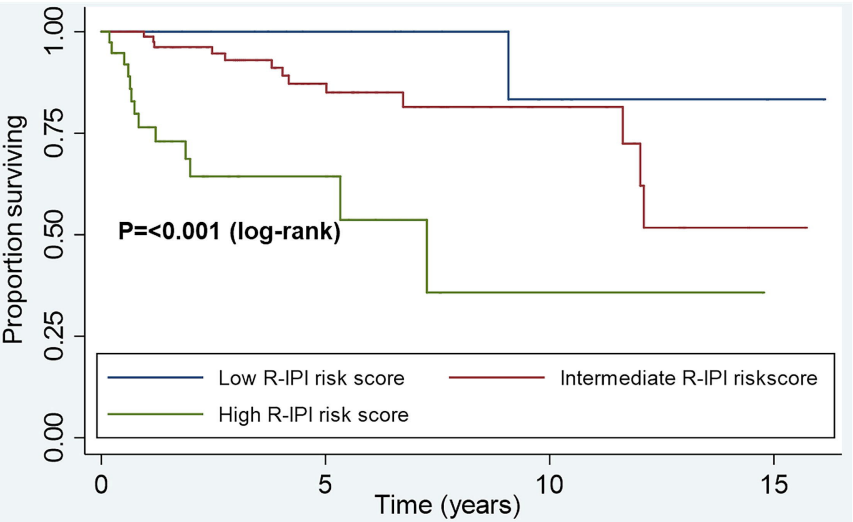


Figure 4A. G3BFL overall survival according to FLIPI risk score.



Number at risk				
FLIPI low	25	13	5	1
FLIPI intermediate	41	15	4	0
FLIPI high	85	33	7	1

Figure 4B. G3BFL overall survival according to R-IPI.



Number at risk				
R-IPI low	24	12	4	1
R-IPI intermediate	90	40	11	1
R-IPI high	38	9	1	0