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Minimal relapse risk and early normalization of survival for patients with Burkitt lymphoma treated with intensive immunochemotherapy: An international study of 264 real-world patients

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Running head: Burkitt lymphoma outcomes following intensive immunochemotherapy

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Abstract

Non-endemic Burkitt lymphoma (BL) is a rare germinal center B-cell derived malignancy with the genetic hallmark of *MYC* gene translocation and with rapid, tumor growth as a distinct clinical feature. To investigate treatment outcomes, loss of lifetime, and relapse risk in adult BL patients treated with intensive immunochemotherapy, retrospective clinic-based and population-based lymphoma registries from six countries were used to identify 264 real-world patients. The median age was 47 years and the majority had advanced stage disease and elevated LDH. Treatment protocols were R-CODOX-M/IVAC (47%), R-hyper-CVAD (16%), DA-EPOCH-R (11%), R-BFM/GMALL (25%), and other (2%) leading to overall response rate of 89%. The 2-year overall survival and event-free survival were 84% and 80%, respectively. For patients in complete remission/unconfirmed, the 2-year relapse risk was 6% but diminished to 0.6% for patients reaching

12 months of post-remission event-free survival (pEFS12). The loss of lifetime for pEFS12 patients was 0.4 (95%CI:-0.7-2) months. In conclusion, real-world outcomes of adult BL are excellent following intensive immunochemotherapy. For pEFS12 patients, the relapse risk was low and life expectancy similar to that of a general population, which is important information for developing meaningful follow-up strategies with increased focus on survivorship and less focus on routine disease surveillance.

Introduction

Non-endemic Burkitt lymphoma (BL) is a rare germinal center B-cell derived malignancy and among the most aggressive types of non-Hodgkin lymphomas (NHL) (Swerdlow *et al*, 2017). The majority of BL patients are diagnosed with advanced stage disease and have extensive extranodal involvement, which can lead to oncologic emergencies such as tumor compression of vital organs and/or life-threatening tumor lysis (Molyneux *et al*, 2012; Dunleavy *et al*, 2013; Castillo *et al*, 2013). However, BL is highly sensitive to chemotherapy and rapid reduction in tumor volume is typically seen within days after commencing treatment (Blum *et al*, 2004). In particular, the outcomes for adult BL have improved dramatically after adopting the intensive multidrug chemotherapy protocols used in pediatric BL or acute lymphoblastic leukemia (ALL) instead of the more conventional NHL regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) (Magrath *et al*, 1984, 1996; Diviné *et al*, 2005; Dave *et al*, 2006; Wästerlid *et al*, 2013; Smeland *et al*, 2004). Inclusion of rituximab in first-line therapy has led to further survival improvements, similarly to other aggressive B-cell lymphomas (Ribrag *et al*, 2016; Rizzieri *et al*, 2014; Barnes *et al*, 2011; Hoelzer *et al*, 2014; Thomas *et al*, 2006; Corazzelli *et al*, 2012; Wästerlid *et al*, 2013). However, intensive multidrug chemotherapy protocols are associated with risk of life-threatening acute toxicities and late complications (Oeffinger *et al*, 2006; Corazzelli *et al*, 2012;

Barnes *et al*, 2011; Hoelzer *et al*, 2014; Ribrag *et al*, 2016). Additionally, the favorable results seen in clinical trials using such treatment protocols do not necessarily apply to the broad population of patients in the routine clinical setting, who may be older, frailer, or have urgent need for treatment excluding them from trial inclusion (Maurer *et al*, 2018).

In the present international study, BL outcomes following treatment with intensive immunochemotherapy regimens are reported together with dynamic survival estimates and relapse risks based on population and clinic-based registries.

Patients and methods

This retrospective study included patients from clinic-based and population-based lymphoma registries in Australia (Sir Charles Gairdner Hospital [Perth]), Canada (BC Cancer Lymphoid Cancer and Leukemia/BMT Program Databases [Vancouver]), Denmark (the Danish Lymphoma Registry [LYFO]), Norway (Health Region South East, Oslo University Hospital), Sweden (the Swedish Lymphoma Registry [SLR]), and the USA (Mayo Clinic [Rochester, Minnesota] and University of Iowa [Iowa City, Iowa]). The registries are described in detail in the Supplementary text. Patient information was retrieved from the registries with additional data abstraction from medical records as necessary. The surveyed time period was 2004-2017, with local differences depending on the structure of the registries.

The study relied on the BL diagnosis made by the treating physicians based on all available clinical information and pathology results. As part of this study and to ensure that the BL diagnosis was made in accordance with central diagnostic criteria used today (Swerdlow *et al*, 2017). local investigators performed additional retrospective reviews of pathology reports to document that the BL diagnosis was made based on the presence of; 1) medium-sized monotonous lymphocytes with diffuse growth pattern, 2) high proliferation rate (KI-67 ≥90% if KI-67 had been performed), 3) typical germinal center B-cell markers, such as CD20+, CD10+, and Bcl6+, on immunohistochemistry, and 4) fluorescence in-situ hybridization (FISH) detected *MYC* translocation (Swerdlow *et al*, 2008). Patients without FISH detected *MYC* translocation were excluded from the present study, to minimize inclusion of patients that would have been classified as unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and BL according to the 2008 WHO classification (Swerdlow *et al*, 2008). However, we acknowledge that BL may still be diagnosed in the absence of *MYC* rearrangements if other clinicopathology features are consistent (Swerdlow *et al*, 2016). Patients meeting diagnostic criteria

for the new provisional BL category with chromosome 11q aberrations without *MYC* translocation were not included (Swerdlow *et al*, 2017).

Adult patients (aged ≥18 years) treated with rituximab-containing dose-intense chemotherapy protocols (mostly but not limited to DA-EPOCH-R [dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin], R-hyper-CVAD [hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, intrathecal (IT) methotrexate, and IT cytarabine alternated with high dose (HD) methotrexate, and cytarabine], R-CODOX-M/IVAC [cyclophosphamide, vincristine, doxorubicin, IT cytarabine, HD methotrexate, IT methotrexate / etoposide, ifosfamide, cytarabine, IT methotrexate], and the R-BFM/GMALL protocol [prednisone, cyclophosphamide, HD methotrexate, dexamethasone, ifosfamide, etoposide, , doxorubicin, vincristine/vindesine, cytarabine, IT methotrexate, IT cytarabine, and IT dexamethasone]) were included in the study. Patients were grouped according to the first intensive treatment they received in an intention-to-treat analysis, but a single cycle of CHOP-like therapy was allowed before initiation of intensive treatment, as this strategy is frequently used to achieve immediate disease control pending final diagnosis. As a rule, disease staging included full body computed tomography (CT) or fluorodeoxyglucose (FDG)- positron emissions tomography (PET)/CT-based imaging, bone marrow biopsy and cytological evaluation of cerebrospinal fluid as part of first IT treatment in patients receiving therapies that included this or if CNS involvement was suspected. Clinical tumor lysis was classified using established criteria (Howard *et al*, 2011).

Response evaluations were performed in accordance with relevant response criteria, depending on the use of CT or FDG-PET/CT-based imaging (Cheson *et al*, 1999, 2007, 2014). As a rule, bone marrow biopsy was repeated as a part of the post-therapeutic response assessment in cases with pre-therapeutic bone marrow involvement.

A subset of the patients included in the present study have been reported in previously published studies, but outcomes of different treatment strategies, documentation of *MYC* translocation, confirmation of response by reviewing medical files, or reporting of novel outcomes measures such as dynamic relapse risks and conditional survival estimates were not part of these studies (Wästerlid *et al*, 2013; Zhu *et al*, 2018). The study was conducted in accordance with national and local regulations for retrospective observational studies.

Statistical analyses

Overall survival (OS) was defined as the time from diagnosis until death from any cause or censoring of patients still alive at end of follow-up, whereas event-free survival (EFS) was defined as the time from diagnosis until unplanned re-treatment, progression/relapse, death or censoring at end of follow-up. Survival probabilities were estimated using the Kaplan-Meier estimator (Kaplan & Meier, 1958). The treatment groups were compared using an inverse probability of treatment weighting (IPTW) approach to adjust for imbalances between the groups (see Supplementary text) (Austin & Stuart, 2015). Because IPTW requires that all treatment groups are represented at every combination of the observed confounders, the imbalances were only adjusted for age as a continuous variable, gender, and stage (I-II vs. III-IV) (Westreich & Cole, 2010). In a sensitivity analysis, we additionally adjusted for performance status (0-1 vs >1), number of extranodal sites, lactate dehydrogenase (LDH) level (elevated vs normal), and the presence of B symptoms. We used the Benjamini-Hochberg method to adjust for multiple testing when comparing the treatment groups (Benjamini & Hochberg, 1995). Cause-specific cumulative incidences of death were estimated using the Aalen-Johansen estimator (Martinussen & Scheike, 2006). The 5-year restricted loss of lifetime (RLOL) was calculated as the area between the BL Kaplan-Meier curve and the general population survival curve obtained using the Ederer I method (Ederer *et al*, 1961) and country-specific life tables retrieved from the Human Mortality Database stratified on age, gender, and calendar year (University of California Berkeley & Max Planck Institute for Demographic Research).

For patients reaching complete remission (CR)/CR unconfirmed (CRu), the post-remission overall survival (pOS), cumulative incidence of relapse, and 5-year RLOL estimates were computed with follow-up measured from the time of response evaluation. The pOS, relapse risk, and the 5-year RLOL were also computed for the subset of patients event-free at 6 (pEFS6) and 12 (pEFS12) months post-CR with follow-up measured from the milestones.

Prognostic factors were examined using univariable and multivariable Cox proportional hazards models for EFS and a score test statistic was used to test for proportional hazards (Grambsch & Therneau, 1994). All analyses were conducted in the statistical programming language R.

Results

Patients and Treatment

A total of 264 patients from 6 different countries (Australia, 18; Canada, 73; Denmark, 61; Norway, 41; Sweden, 56; USA, 15) fulfilled the criteria of classical BL and were analyzed in the present

study (Figure S1). Baseline clinicopathological characteristics of the included patients are shown in Table 1 (see Table S1 for characteristics stratified on country). The most frequently used intensive chemotherapy protocol was R-CODOX-M/IVAC (47% of the patients). R-BFM/GMALL and R-hyper-CVAD were used in 66 (25%) and 41 (16%) of the patients, respectively, while 28 (11%) received DA-EPOCH-R. Treatment de-escalation was chosen for 11 (4%) patients and 9 (3%) changed to another intensive chemotherapy regimen (Figure S1). Thirteen patients received consolidative bone marrow transplant (BMT) after treatment with R-CODOX-M/IVAC. Country-specific distributions of first-line therapy are provided in Table S2 and clinicopathologic differences between treatment groups are shown in Table S3. Among the 178 (67%) patients for whom data on clinical tumor lysis syndrome were available, 32 (18%) patients developed clinical tumor lysis upon initiation of therapy. All tumor lysis patients presented with high-risk disease including advanced stage and elevated LDH.

The overall response rate was 89% (85% CR/CRu and 4% partial remission [PR]), with 108 patients (44%) response assessed using FDG-PET technology. The median follow-up for the entire patient cohort computed by the reverse Kaplan-Meier method was 54 months (95% CI, 50-62) and the estimated 2-year OS and EFS were 84% (95% CI, 79%-88%) and 80% (95% CI, 75%-85%), respectively (Figure 1). The 2-year OS of patients <40, 40-59, and ≥60 years was 92% (95% CI, 87%-97%), 83% (95% CI, 75%-91%), and 72% (95% CI, 61%-83%), respectively (Figure 1). In adolescents and young adults (AYAs, <40 years of age), particularly high OS and EFS was observed among patients aged 18-21 (2-year OS and EFS, 100%) and 22-30 (2-year OS and EFS, 98% and 93%, respectively, Figure S2). Clinical factors associated with unfavorable EFS and OS in univariable analyses were age and elevated LDH. Both retained significance in multivariable analyses (Table S4 and S5). The 2-year EFS for patients with stage III-IV disease and elevated LDH was 73% (95% CI, 66%-80%). Among the subset of patients with CNS involvement at diagnosis (n=21), the 2-year OS and EFS were 80% (95% CI, 63%-98%) and 70% (95% CI, 50%-90%), respectively.

Outcomes after response evaluation

For patients in CR/CRu following intensive immunochemotherapy with available date of response assessment (n=223), the 2-year cumulative relapse risk from response assessment was 6% (95% CI, 3%-10%), while patients reaching pEFS6 (n=202) and pEFS12 (n=189) had a 2-year cumulative

relapse risk of 3% (95% CI, 0%-5%) and 0.6% (95% CI, 0%-2%), respectively (Figure 2). The corresponding 2-year pOS estimates were 92% (95% CI, 89%-96%), 96% (95% CI, 93%-99%), and 98% (95% CI, 95%-100%) from response assessment, pEFS6, and pEFS12, respectively (Figure S3). The 5-year RLOL was 4 months (95% CI, 2-6) from the time of response assessment, while patients reaching pEFS6 and pEFS12 had a 5-year RLOL of 2 (95% CI, 0.2-3) and 0.4 (95% CI, -0.7-2) months, respectively.

RLOL estimates stratified according to baseline clinicopathologic features are reported in Figure 3. From the time of response assessment, low-risk features such as limited stage, performance status 0-1, age <40, and normal LDH values were associated with lower RLOL. However, the impact of high-risk features on RLOL diminished as time in CR/CRu elapsed. This effect was especially pronounced for performance status. The 2-year OS from response evaluation in patients with progressive disease (n=13) was 8% (95% CI, 0%-22%, Figure 4A). Patients who relapsed after achieving initial CR/CRu (n=14) had dismal outcomes with 2-year post-relapse OS of 14% (95% CI, 0%-33%, Figure 4B).

Outcomes according to intensive immunochemotherapy protocols

A global log-rank test did not detect any significant OS difference between the treatment groups (P=0.2, Figure 5A). Survival curves adjusted for age, gender, and stage are provided in Figure 5B. Although we found significantly improved OS among patients treated with R-CODOX-M/IVAC compared to R-hyper-CVAD (P=0.04) after adjusting for age, gender, and stage, these were not significantly different after adjusting for multiple comparisons (P=0.24). No other OS differences were observed between the treatment groups (Table S6). This result was similar for EFS (Figure S4 and Table S6) and a sensitivity analysis also adjusting for performance status, extranodal sites, B symptoms, and LDH did not change the conclusion (Figure S5). The 28 patients treated with DA-EPOCH-R had 2-year OS and EFS of 77% (95% CI, 61%-93%, Figure 5A) and 74% (95% CI, 57%-91%, Figure S2A), respectively.

Discussion

In the present international study, we investigated real-world outcomes of newly diagnosed BL patients treated with intensive chemotherapy regimens and rituximab. We demonstrated a high overall response rate translating into excellent OS with minimal loss of residual lifetime, even for

patients with CNS involvement at diagnosis. The relapse risk was minimal after 12 months in remission, an important finding when it comes to developing rational disease surveillance strategies and survivorship care plans.

BL is rare in the Western World with an estimated incidence rate in 2008 of 2.36 and 5.95 per 1,000,000 person-years for females and males, respectively (Costa *et al*, 2013). This, combined with the aggressive clinical presentation and urgent need for treatment, make large randomized trials challenging. The use of intensive multidrug chemotherapy regimens inspired by those used for pediatric ALL are effective in BL, but toxicity limits their application to adult patients with BL (Costa *et al*, 2013). However, Margrath et al. reported comparable efficacy and toxicity for children and adults (aged 18-59) in a study of 41 BL patients treated with CODOX-M/IVAC (Magrath *et al*, 1996). Other single arm phase II studies and multicenter retrospective studies of ALL(-like) treatment regimens have confirmed the efficacy of this strategy in adults (Soussain *et al*, 1995; Thomas *et al*, 1999; Hoelzer *et al*, 1996; Diviné *et al*, 2005; Mead *et al*, 2002). Common toxicities include myelosuppression and mucositis and toxic deaths were reported in most studies (Diviné *et al*, 2005; Soussain *et al*, 1995; Thomas *et al*, 1999; Hoelzer *et al*, 1996; Mead *et al*, 2002). In the present study, outcomes were excellent despite a median age of 47 years, and consistent with previous studies, age was significantly associated with OS and EFS (Thomas *et al*, 1999; Diviné *et al*, 2005; Zhu *et al*, 2018). The AYA patient population had excellent outcomes with 2-year OS of 92%. Of note, consolidative BMT was given to 13 patients treated with R-CODOX-M/IVAC, but this did likely not impact outcomes (Zhu *et al*, 2018).

Less intensive treatments such as CHOP or CHOEP are associated with poor outcomes in BL (Smeland *et al*, 2004; Wästerlid *et al*, 2013). In a retrospective Norwegian cohort study of 49 BL patients, investigators reported poorer outcomes among patients treated with CHOP and methotrexate, relative to BFM (5-year progression-free survival [PFS] was 31% and 74%, respectively) (Smeland *et al*, 2004), and these results were confirmed in a Danish-Swedish population-based study of patients diagnosed in the period 2000-2009 (Wästerlid *et al*, 2013).

Several groups have reported modest improvements from the addition of rituximab to first-line treatment of BL in phase II studies (Evens *et al*, 2013; Intermesoli *et al*, 2013; Hoelzer *et al*, 2014; Thomas *et al*, 2006). The benefit of rituximab was confirmed in the only randomized trial of adult BL with significantly higher 3-year EFS in rituximab treated patients (75% vs. 62%) (Ribrag *et al*,

2016). Similar outcomes (2-year EFS, 80%) were observed in the present cohort of real-world patients suggesting that the clinical trial result can be extrapolated to daily clinical practice.

DA-EPOCH-R is less dose-intensive than typical ALL(-like) regimens, but still highly efficacious for BL in two recent phase II trials of 30 and 113 patients with or without HIV (Dunleavy *et al*, 2013; Roschewski *et al*, 2017). Toxicity was manageable with fever and neutropenia requiring hospital admissions in 26/116 treatment cycles and with few cases of mucositis. Despite the inclusion of patients >85 years of age, the 2-year OS of HIV-negative patients (n=19) was 100% in the pivotal phase 2 study of DA-EPOCH in BL, while patients in the NCI9177 study had a 2-year OS of 86% with DA-EPOCH using an interim PET adapted treatment strategy (Dunleavy *et al*, 2013; Roschewski *et al*, 2017). Patients treated with DA-EPOCH-R in our study (n=28) had more high-risk features than the patients enrolled in the study by Dunleavy et al. (Table S7). These differences may explain why the 2-year OS and EFS of 77% (95% CI 61%-93%) and 74% (95% CI 57%-91%) in the present study were lower than the 100% OS and 95% PFS reported by Dunleavy et al. (Dunleavy *et al*, 2013).

The event-free survival at 24 months end-point and others like this provide an intuitive framework for patient counselling and may also serve as surrogate end-points in clinical trials (Maurer *et al*, 2014; Shi *et al*, 2018). In the present study, we demonstrated normalization of survival and a negligible relapse risk for patients with BL remaining in remission 12 months after completing intensive immunochemotherapy. Although late disease relapse was rare in this study, the occurrence of late toxicity remains a concern and provides potential rationale for changing focus from disease surveillance and cost-ineffective screening for asymptomatic relapse to improving survivorship in these heavily treated patients.

The main strength of the present multicenter study was the inclusion of a large number of real-world adult BL patients ensuring that our results are generalizable to a broad population of patients. We also used novel, patient-centered outcome measures to facilitate more meaningful patient counselling in clinical practice. However, the study also has important limitations inherent to the observational design. Therapies were selected at the discretion of the attending physician, and treatment-specific outcome differences can be confounded by selection bias. IPTW used in the present study may overcome this to some extent, but unknown sources of bias and limited number of patients in each subgroup limits the strength of our conclusions. No data on dose intensity was collected, but it is likely that some patients, in particular patients ≥60 years, received dose-modified regimens or shortened duration of treatment due to toxicities - an approach associated with inferior

outcomes when compared to younger adults in most studies (Intermesoli *et al*, 2013; Hoelzer *et al*, 2014; Lacasce *et al*, 2004; Corazzelli *et al*, 2012; Thomas *et al*, 2006; Ribrag *et al*, 2016; Mead *et al*, 2008; Zhu *et al*, 2018). Consistently, in the current study patients ≥60 years of age had significantly greater loss of lifetime. HIV or immunodeficiency status was not consistently available, but sites contributing to the study were from low endemic HIV areas making sporadic BL the main driver of our results. Furthermore, highly active antiretroviral therapy was available during the surveyed time period, and this has increased survival of HIV-associated BL to that of sporadic BL (Intermesoli *et al*, 2013; Ribera *et al*, 2013; Rodrigo *et al*, 2012; Oriol *et al*, 2008; Dunleavy *et al*, 2013; Barnes *et al*, 2011; Zhu *et al*, 2018).

Based on this study, we conclude that intensive multidrug immunochemotherapy protocols are highly effective for achieving durable remissions in adult BL patients. Early normalization of survival and a negligible relapse risk for patients in remission for 12 months can reassure BL patients and their families as well as guide appropriate use of limited health care resources for disease surveillance. However, the dismal outcomes among patients who are refractory or relapse highlight an unmet medical need in this subgroup. Future research efforts should focus on inclusion of novel agents and/or further refined dynamic risk adapted treatment strategies based on early therapy response to reduce treatment toxicity without compromising efficacy.

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Author contributions

TCEG, FE, KBS, ASG, GT, CYC, and LHJ initiated and designed the study.

FE, KBS, TW, JHC, JMJ, PLJ, AKØ, HH, YNB, JHG, JB, DM, IL, KES, KC, GT, TMH, KWS, KYZ, ASG, CYC, and TCEG aquired data.

LHJ, FE, MJM, and TCEG did the statistical analysis. All authors interpreted the data, drafted and reviewed the manuscript, and approved the final manuscript.

Conflict of interests

TCEG: Employment by Roche since January 1st 2019. The present research was done as part of ongoing affiliation with Aalborg University Hospital/Aalborg University.

DM: Honoraria from Roche, Merck, Bristol-Myers Squibb, and Takeda.

CYC: Advisory for Roche, Janssen, Takeda, MSD, Gilead, Bristol Myers Squibb, and AstraZenecca. Research funding from Celgene, Roche, Abbvie. Travel expenses from Roche and Amgen.

JUJ: Advisory for Gilead and Roche. Travel expenses from Gilead and Roche.

KES: Advisory for Roche. Research support from Janssen-Cilag.

HH: Advisory for Novartis, Nordic Nanovector, Gilead, Takeda, Roche, and Celgene.

MJM: Advisory for Morphosys. Research funding from Celgene and Nanostring.

LHJ: Honoraria from Takeda.

AG: Institutional research support from Roche, Lundbeck, and Janssen. Honoraria from AbbVie, Janssen, Celgene, and Novartis.

FE: Consulting for Roche.

Table 1: Demographics, treatment information, and final response evaluation for 263 Burkitt lymphoma patients treated with intensive immunochemotherapy.

	All patients (n = 264)
Median age (range)	47(18-81)
Male patients	200(76)
Ann Arbor stage III-IV, n(%)	205(78)
ECOG performance > 1, n(%)	91(34)
Elevated LDH, n(%)	190(73)*
Extranodal disease, n(%)	226(86)
- Bone(marrow)	111(42)
- Central nervous system	21(8)
B symptoms, n(%)	146(57)*

Country, n(%)	
- Australia	18(7)
- British Columbia	73(28)
- Denmark	61(23)
- Norway	41(16)
- Sweden	56(21)
- USA	15(6)
Primary treatment, n(%)	
- R-CODOX-M/IVAC	124(47)
- R-Hyper-CVAD	41(16)
- R-DA-EPOCH	28(11)
- R-BFM/GMALL	66(25)
- Other	5(2)
PET or PET/CT-based response, n(%)	108(44)*
Response evaluation, n(%)	
- CR/CRu	224(85)
- PR	10(4)
- Less than PR	30(11)

* Missing information on a subset of the patients

R-CODOX-M/IVAC cyclophosphamide, vincristine, doxorubicin, IT cytarabine, HD methotrexate, IT methotrexate / etoposide, ifosfamide, cytarabine, IT methotrexate plus rituximab

R-hyper-CVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, IT methotrexate, and IT cytarabine alternated with high dose (HD) methotrexate, and cytarabine plus rituximab

DA-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab

R-BFM/GMALL: prednisone, cyclophosphamide, HD methotrexate, dexamethasone, ifosfamide, etoposide, ±teniposide, doxorubicin, vincristine, cytarabine, ±vindesine, IT methotrexate, IT cytarabine, and IT dexamethasone plus rituximab

Figure legends

Figure 1: Overall (A) and event-free survival (B) following intensive immunochemotherapy for all patients and stratified according to age (<40, 40-59, and ≥60 years).

Figure 2: Cumulative incidence of relapse for patients in CR/CRu after intensive immunochemotherapy with time measured from response evaluation (n = 223), pEFS6 (n = 202), and pEFS12 (n = 189).

Figure 3: Five-year restricted loss of lifetime for Burkitt lymphoma patients in CR/CRu after intensive immunochemotherapy stratified by clinical subgroup. No females or patients between 40 and 59 years died after achieving the pEFS12 milestone.

Figure 4: Overall survival of A) 13 BL patients responding with progressive disease to primary intensive immunochemotherapy and B) 14 BL patients relapsing after treatment with intensive immunochemotherapy.

Figure 5: A) overall survival stratified on primary treatment regimen and B) treatment-specific overall survival adjusted for age, gender, and stage.

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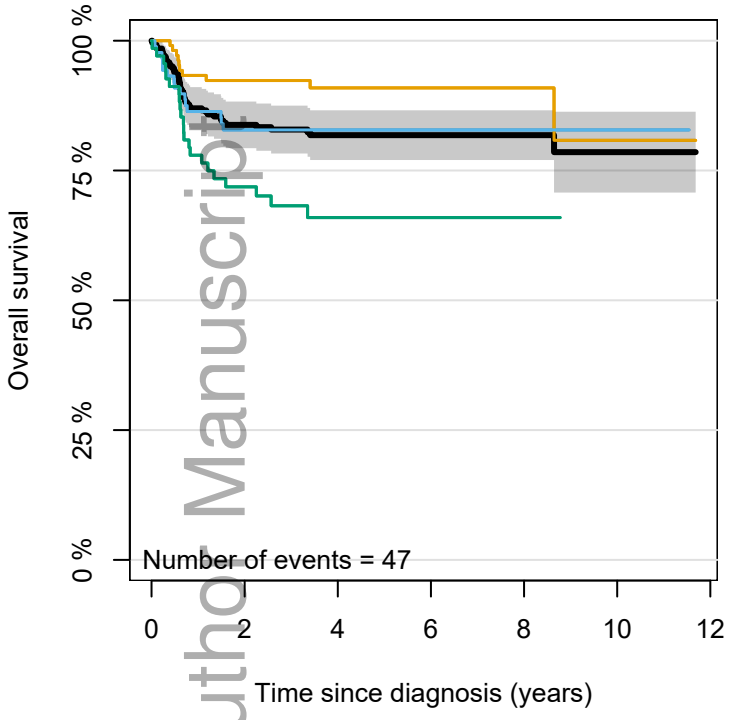
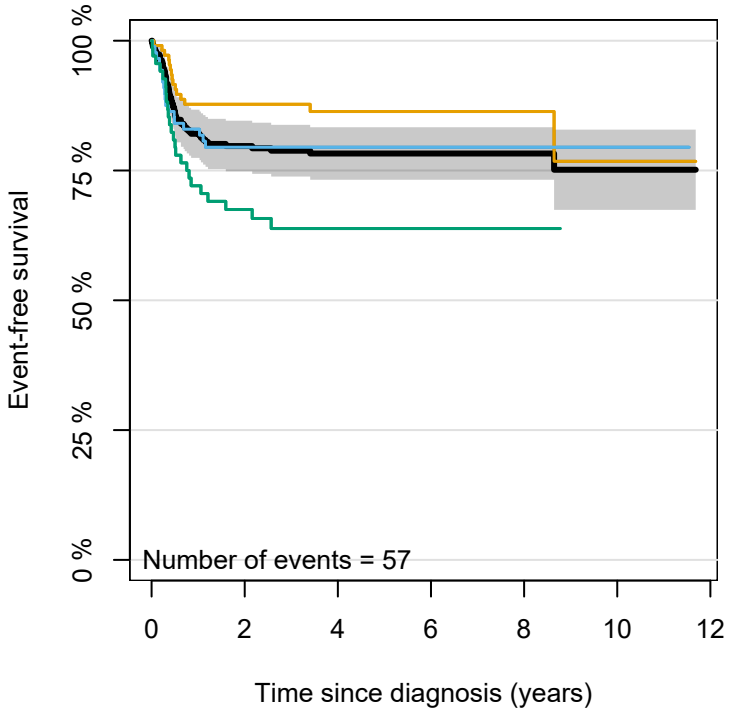
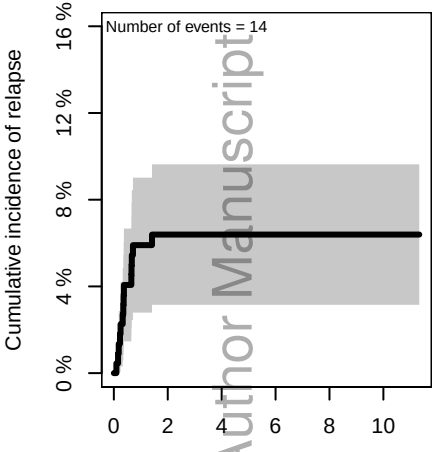


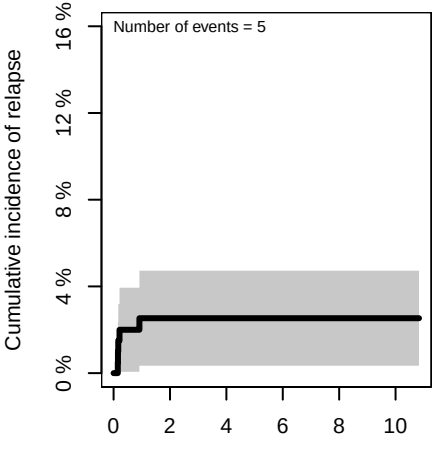


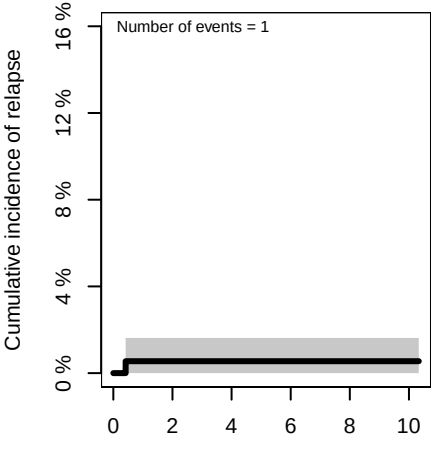
<40 years	108	88	56	28	14	2	0
40-59 years	88	69	50	26	18	10	0
≥60 years	68	42	24	10	3	0	0

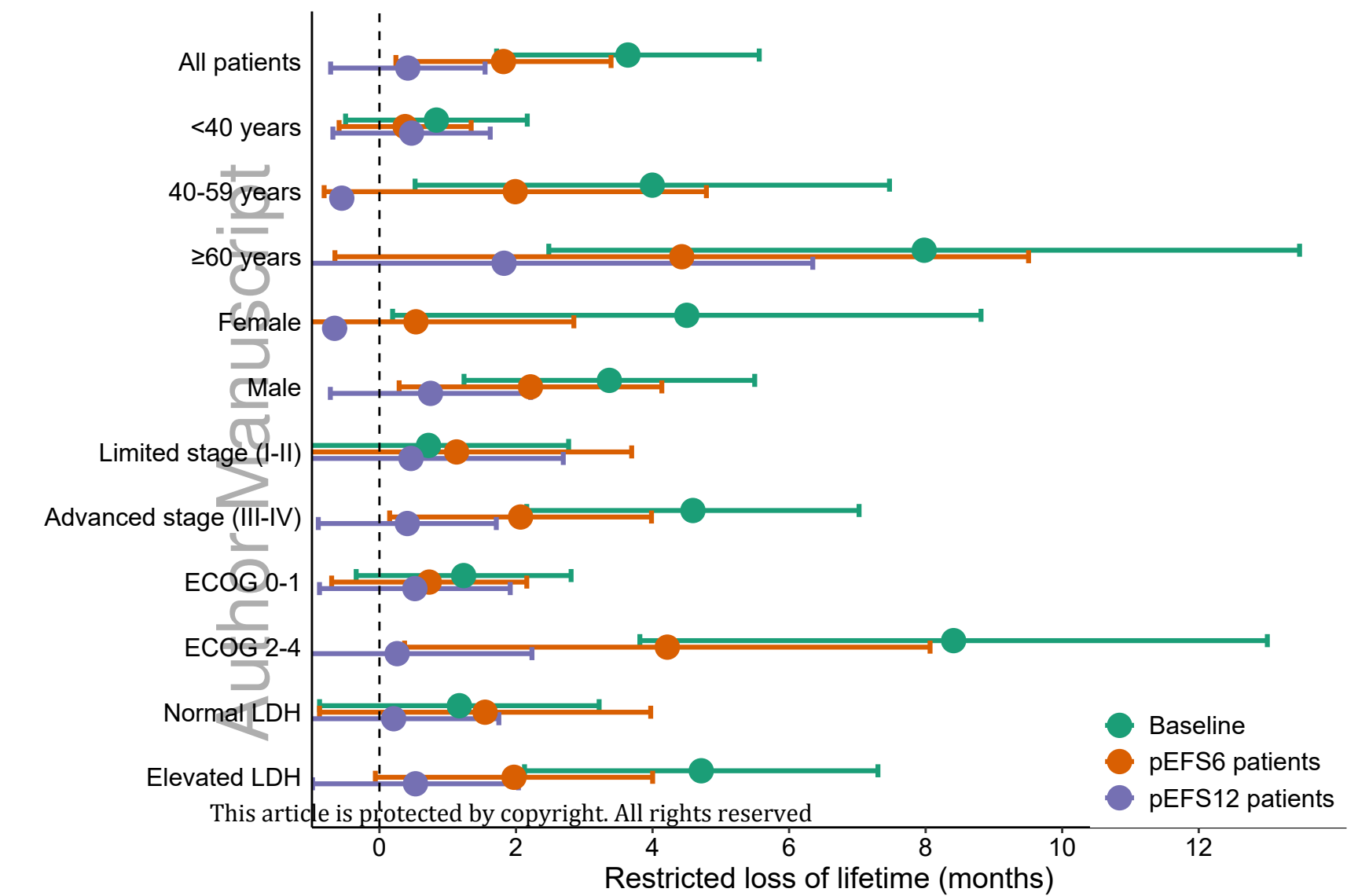
<40 years	108	84	54	27	14	2	0
40-59 years	88	66	48	26	18	10	0
≥60 years	68	39	23	9	3	0	0

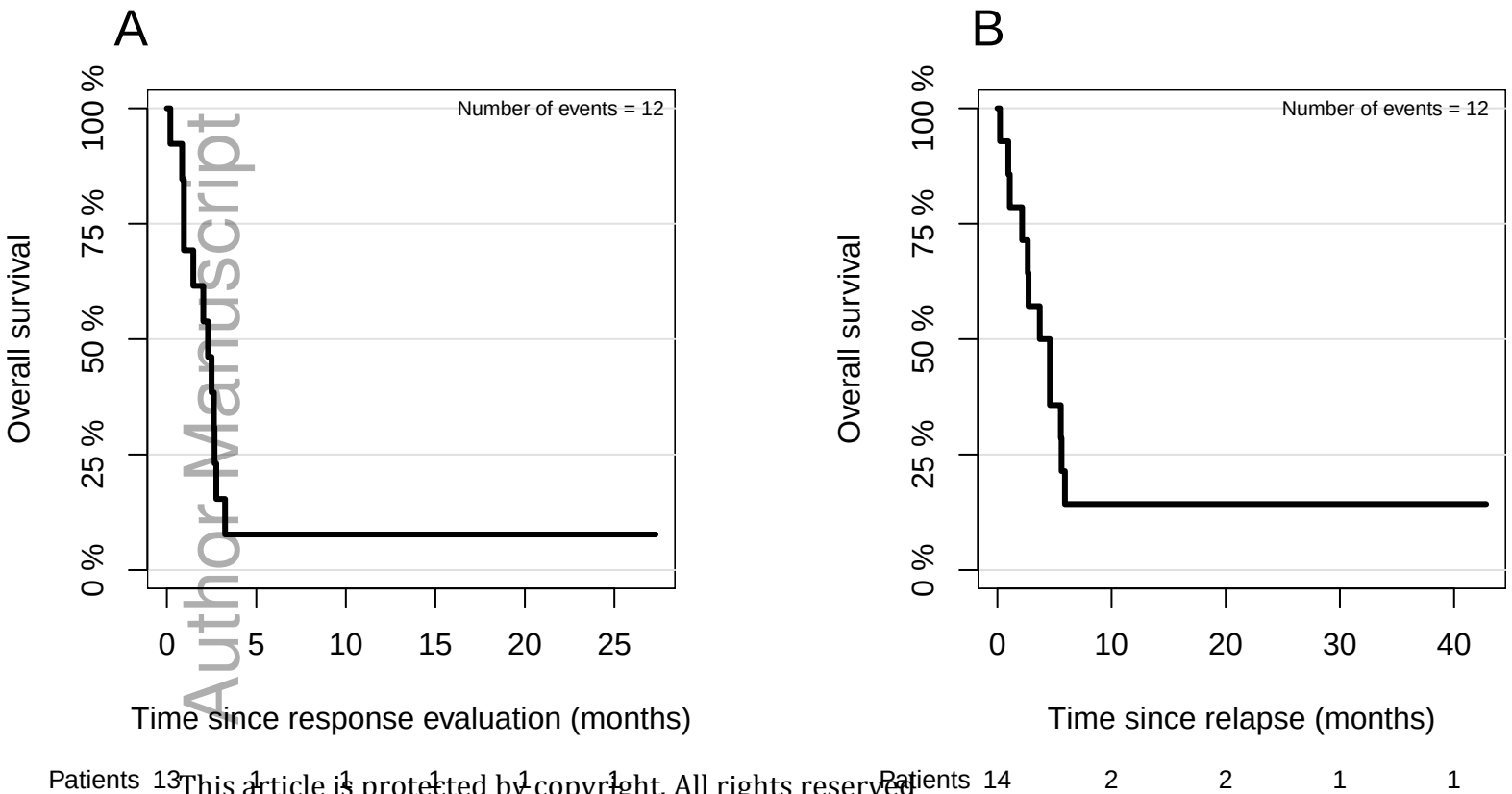
All patients <40 years 40-59 years ≥60 years

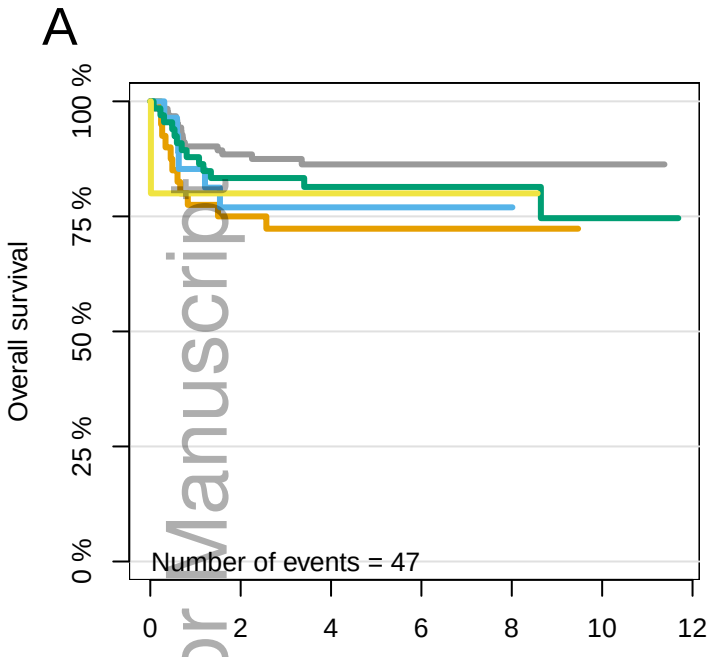


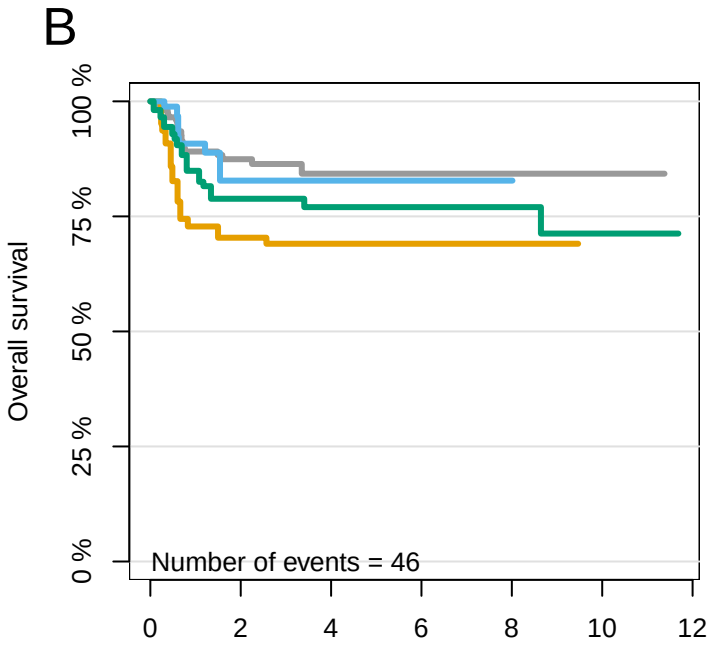












CODOX−M/IVAC	124	96	59	33	17	5	0
Hyper−CVAD	41	29	20	7	2	0	0
DA−EPOCH	28	17	10	3	1	0	0
BFM/GMALL	66	53	38	19	14	7	0
Other	5	4	3	2	1	0	0

CODOX−M/IVAC	124	96	59	33	17	5	0
Hyper−CVAD	41	29	20	7	2	0	0
DA−EPOCH	28	17	10	3	1	0	0
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